DIAGNOSIS AND TREATMENT OF COMMON VIRAL INFECTIONS

Chapter 26

HERPES SIMPLEX VIRUS (HSV)

Herpes simplex virus type 1 (HSV-1) accounts for most oral, labial and ocular infections and HSV-2 for most genital infections, although there is considerable overlap in these distributions

ORAL-LABIAL HSV INFECTION

PRIMARY ORAL-LABIAL HSV INFECTION

The majority of primary infections are subclinical. Symptomatic infection is usually in children between one and five years of age and presents as gingivostomatitis or pharyngitis. In adults, symptomatic infection may present as pharyngitis or a mononucleosis-like syndrome. A laboratory diagnosis is made by means of an HSV PCR on a swab taken from the lesion (e.g. the base of a deroofed ulcer or vesicle fluid). Treatment significantly decreases the duration and severity if given within 72 hours of onset. If a patient presents after 72 hours with ongoing development of new lesions or significant pain, antiviral therapy should still be offered.

TREATMENT: PRIMARY ORAL-LABIAL HSV INFECTION

Acyclovir 400 mg PO 8 hourly for 7–10 days

OR

Valacyclovir 1000 mg PO 12 hourly for 7–10 days

OR

If the patient is unable to swallow: Acyclovir 5 mg/kg/dose IV 8 hourly for 7–10 days

RECURRENT ORAL-LABIAL HSV INFECTION

HSV reactivation may lead to cutaneous or mucocutaneous recurrences known as herpes labialis or fever blisters. A laboratory diagnosis is made, if needed, by means of an HSV PCR on a swab taken from the lesion (e.g. the base of a deroofed ulcer or vesicle fluid).

Management of reactivated infections may include:

- No treatment: occasional episodes with mild symptoms
- Episodic therapy: useful in patients with prodromal symptoms where it must be initiated quickly to be effective
- Chronic suppressive therapy: frequent recurrences that are bothersome to the patient (significant pain and disfiguring lesions), especially in patients without a specific prodrome

Topical acyclovir generally should be avoided since it provides only modest benefit and needs to be applied two to four hours for four to five days.

TREATMENT: RECURRENT ORAL-LABIAL HSV INFECTION

EPISODIC TREATMENT

Acyclovir 800 mg PO 8 hourly for 2 days

OR

Valacyclovir 2 g PO 12 hourly for 1 day

CHRONIC SUPPRESSIVE TREATMENT

Acyclovir 400 mg PO 12 hourly

OR

Valacyclovir 500 mg PO once daily

GENITAL HERPES SIMPLEX VIRUS INFECTION

PRIMARY GENITAL HSV INFECTION

Clinically presentation may include painful genital ulcers, pruritus, dysuria, fever, tender inguinal lymphadenopathy, and headache. In certain cases, patients may be asymptomatic or have only mild symptoms. All patients with primary genital herpes should receive antiviral therapy. Antiviral therapy significantly decreases the duration and severity of disease if commenced within 72 hours of the onset of symptoms. Topical antiviral therapy offers little clinical benefit.

TREATMENT: PRIMARY GENITAL HSV INFECTION

Acyclovir 400 mg PO 8 hourly for 7–10 days

OR

Valacyclovir 1 g PO 12 hourly 7–10 days

RECURRENT GENITAL HSV INFECTION

Treatment for recurrent genital infection can be given as either episodic or as chronic suppressive therapy:

- Episodic treatment is started during the prodrome or within one day after the onset of lesions. Severe genital disease or complications that necessitate hospitalisation (e.g. disseminated infection, pneumonitis, or hepatitis) or CNS complications (e.g. meningoencephalitis) require prolonged intravenous acyclovir treatment.
- Suppressive treatment may be indicated for frequent (usually more than six episodes per year), severe recurrences or in HSV-infected patients in whom the sexual partner is uninfected. Suppression reduces recurrences by 70–80%, but transmission may still occur. Treatment may be interrupted every six months to determine the natural history of the disease, but may be restarted in the event of further recurrences. Safety and efficacy have been documented among patients receiving chronic suppressive treatment with acyclovir for as long as six years and with valacyclovir for one year. In HIV-infected patients higher and/or more frequent doses are required.

TREATMENT: RECURRENT GENITAL HSV INFECTION

EPISODIC TREATMENT: HIV-UNINFECTED

Acyclovir 800 mg PO 8 hourly for 2 days

OR

Valacyclovir 500 mg PO 12 hourly for 3 days

OR

Valacyclovir 1 g PO once a day for 5 days

EPISODIC TREATMENT: HIV-INFECTED

Acyclovir 400 mg PO 8 hourly for 5–10 days

OR

Valacyclovir 1 g PO 12 hourly for 5–10 days

SEVERE RECURRENT GENITAL HSV INFECTION

Acyclovir 5–10 mg/kg IV 8 hourly for 2–7 days or until clinical improvement, followed by oral antiviral therapy to complete 10 days total therapy

CHRONIC SUPPRESSIVE TREATMENT: HIV-UNINFECTED

Acyclovir 400 mg PO 12 hourly for 6 months

OR

Valacyclovir 500 mg PO once a day for 6 months*

OR

Valacyclovir 1 g PO once a day for 6 months

*May be less effective in very frequent recurrences (≥ 10 episodes per year)

CHRONIC SUPPRESSIVE TREATMENT: HIV-INFECTED

Acyclovir 400–800 mg PO 8–12 hourly for 6 months

OR

Valacyclovir 500 mg PO 12 hourly for 6 months

GENITAL HERPES SIMPLEX VIRUS INFECTION IN PREGNANCY

Transmission of HSV to neonates usually occurs during labour and delivery. The risk of transmission to a neonate from an infected mother who develops a primary genital herpes infection near the time of delivery is high (30–50%). The risk of transmission is low (< 1%) for recurrent maternal genital herpes or primary genital HSV occurring during the first half of pregnancy.

Treatment with oral acyclovir can be given to pregnant women with primary genital herpes or recurrent herpes and should be administered IV to pregnant women with severe HSV infection. Suppressive treatment is recommended starting at 36 weeks of gestation in women with recurrent genital herpes.

SUPPRESSIVE TREATMENT IN PREGNANCY STARTING AT 36 WEEKS GESTATION

Acyclovir 400 mg PO 8 hourly

OR

Valacyclovir 500 mg PO 12 hourly

NEONATAL HSV

Neonatal infection usually results from exposure to HSV in the mother's genital tract during delivery. Three different clinical presentations are described: infection localised to the skin, eye and mucosa (SEM); CNS infection with or without SEM, and disseminated infection, which presents with a sepsis-like syndrome. Visceral infection carries a mortality risk in excess of 80%.

TREATMENT OF NEONATAL HSV

All forms of neonatal HSV should be treated with acyclovir 20 mg/kg/dose IV 8 hourly (dose 12 hourly for preterm neonates < 33 weeks).

Treatment duration is 14 days for localised disease (SEM) or 21 days for disseminated or CNS disease.

Following parenteral treatment for all forms of neonatal HSV disease (SEM, CNS, and disseminated disease) suppressive therapy with oral acyclovir 300 mg/m^2 per dose 8 hourly for 6 months should be given. This has been demonstrated to improve neurological outcomes and reduce the risk of recurrences.

ORGAN SPECIFIC HSV INFECTIONS

ENCEPHALITIS

Herpes simplex virus is the most common cause of sporadic encephalitis. About one-third of patients with encephalitis have a primary HSV infection and two-thirds have a recurrent infection. Typical clinical features include the rapid onset of headache, fever and vomiting, progressing to the development of focal neurological abnormalities (typically temporal lobe dysfunction with language, behavioural abnormalities and memory impairment), and focal or generalised seizures.

The laboratory diagnosis is made by means of an HSV PCR on CSF. It is important to note that the CSF HSV PCR may be negative early in the course of the infection and repeat testing is advised 3–7 days later where indicated.

Treatment should be given as soon as the condition is suspected, and prior to obtaining the PCR results, since delaying treatment leads to significant neurological sequelae. The duration of therapy in adults and children is 14–21 days. It is recommended to continue for 21 days as the shorter duration may be associated with subsequent relapse.

TREATMENT: HSV ENCEPHALITIS

Preterm neonates < 33 weeks: Acyclovir 20 mg/kg/dose IV 12 hourly for 21 days, followed by 6 months of oral suppressive therapy

Neonate ≥ 33 weeks: Acyclovir 20 mg/kg/dose IV 8 hourly for 21 days, followed by 6 months of oral suppressive therapy

Adults and children: Acyclovir 10 mg/kg IV 8 hourly for 14–21 days

The duration of therapy in adults and children is 14–21 days. It is recommended to continue for 21 days as the shorter duration of treatment increases the risk of subsequent relapse.

HSV HEPATITIS

HSV hepatitis is a fulminant disease that is usually fatal in untreated patients. Those at risk include neonates, immunosuppressed patients (e.g. on corticosteroids, with HIV infection, cancer or myelodysplastic syndromes) and pregnant women. Diagnosis can be difficult, with non-specific signs and symptoms, e.g. abdominal pain, nausea and diarrhoea. HSV hepatitis should be suspected when the triad of high fever, leukopenia, and a transaminitis is present. The diagnosis is made by means of an HSV PCR on a blood sample.

TREATMENT: HSV HEPATITIS

Acyclovir 10 mg/kg IV 8 hourly for 14 days

HSV OESOPHAGITIS

HSV esophagitis is usually seen in immunocompromised patients but can occasionally be seen in immunocompetent patients as well. The diagnosis is made by endoscopic findings, confirmed by histopathological examination and HSV PCR on biopsy specimens from the observed lesions.

TREATMENT: HSV OESOPHAGITIS

ABLE TO TAKE ORAL MEDICATION

Immunocompromised patients: Acyclovir 400 mg PO five times a day for 14–21 days

Immunocompetent patients: Acyclovir 400 mg PO 8 hourly for 7–10 days

SEVERE ODYNOPHAGIA OR DYSPHAGIA (UNABLE TO TAKE ORAL MEDICATION)

Acyclovir 5 mg/kg IV 8 hourly (switch to oral therapy when possible to complete their therapeutic course)

HSV RESPIRATORY TRACT INFECTIONS

Children may develop epiglottitis or laryngitis which in most cases resolves within 10–14 days without complications. HSV-1 pneumonitis is uncommon and mostly seen in immunocompromised patients. HSV recovered from the respiratory tract may be difficult to interpret as it may represent a true bronchopneumonitis, HSV contamination from the oropharynx, or local tracheobronchial reactivation without parenchymal involvement.

TREATMENT: HSV PNEUMONITIS

Acyclovir 10 mg/kg IV 8 hourly for 14 days

HSV EYE INFECTIONS

Refer to the chapter 'Infections of the eye' for further information.

HSV SKIN MANIFESTATIONS

Herpes simplex virus can cause infection anywhere on the skin. Common skin infections include:

- **Herpetic whitlow:** HSV infection of the finger can occur as a result of autoinoculation from oral or genital herpes infections.
- **Herpes gladiatorum:** Usually occurs among wrestlers and rugby players and involve the face, neck and arms
- **Eczema herpeticum:** Usually occurs in patients with atopic dermatitis taking immunosuppressive treatment. This is a dermatological emergency which requires systemic treatment with intravenous acyclovir as it can spread rapidly.

DISSEMINATED HSV INFECTIONS

HSV may cause disseminated infections, typically in immunocompromised patients and neonates. However, approximately 25% of disseminated infections occur in immunocompetent individuals including pregnant patients. Viraemia may be a result of either a primary infection or reactivation of a latent infection. Systemic manifestations include oesophagitis, hepatitis and a pneumonitis. A laboratory diagnosis is made by means of an HSV PCR on a blood specimen.

TREATMENT: DISSEMINATED HSV

Acyclovir 10 mg/kg IV 8 hourly for 14 days
If CNS infection is suspected, treat for up to 21 days

VARICELLA ZOSTER VIRUS

PRIMARY INFECTION: VARICELLA (CHICKENPOX)

IMMUNOCOMPETENT CHILDREN AND ADOLESCENTS

- Oral antiviral therapy is not recommended for children ≤ 12 years of age
- Oral antiviral therapy must be given to immunocompetent children and adolescents at risk of complications:
  - Children ≥ 13 years of age (more likely to have severe infections compared to younger children)
  - Secondary cases in household contacts
  - Patients with chronic cutaneous or pulmonary disorders
  - Children taking intermittent oral or inhaled steroid therapy
  - Individuals taking chronic salicylates

IMMUNOCOMPETENT ADULTS

Oral antiviral therapy must be given to all immunocompetent adults with uncomplicated infections even if they have been previously vaccinated. Antiviral therapy is most beneficial if started within 24 hours of symptom onset but should be given to any patient with evidence of ongoing disease (e.g. active skin lesions). All pregnant women must be give antiviral therapy as they are at high risk for complicated infections.

IMMUNOCOMPROMISED PATIENTS

Immunocompromised patients (e.g. HIV-infected, malignancies, chronic steroid use) must be treated with antiviral therapy. Most patients should receive initial intravenous acyclovir which is continued until no new lesions develop and then transitioned to oral therapy until all the lesions have crusted.

COMPLICATED INFECTIONS

Patients with complicated infections such as severe hepatitis, pneumonia and encephalitis require intravenous antiviral therapy. Individuals who have a more rapid response to treatment (e.g. significant improvement in symptoms and no new lesions) can be transitioned to oral therapy to complete the treatment course. For the management of eye related complications refer to the chapter 'Infections of the eye' for further information.

TREATMENT: PRIMARY VARICELLA INFECTION (CHICKENPOX)

CHILDREN: ≥ 2 YEARS WITH NORMAL RENAL FUNCTION

Acyclovir 20 mg/kg per dose (maximum dose 800 mg) PO 6 hourly for children aged 2–12 years and for adolescents

OR

Valacyclovir 20 mg/kg per dose (maximum dose 1000 mg) PO 8 hourly

Treat for 5 days

IMMUNOCOMPETENT ADULTS

Acyclovir 800 mg PO five times a day

OR

Valacyclovir 1 g PO 8 hourly

Treat for 5–7 days

IMMUNOCOMPROMISED PATIENTS AND PATIENTS WITH DISSEMINATED DISEASE (HEPATITIS, PNEUMONIA, ENCEPHALITIS)

CHILDREN ≥ 1 YEAR OF AGE AND ADOLESCENTS

Acyclovir 1500 mg/m^2 IV per day in three divided doses for 7–10 days

OR

Acyclovir 10 mg/kg IV 8 hourly for 7–10 days

ADULTS

Acyclovir 10 mg/kg IV 8 hourly for 7–10 days

HERPES ZOSTER (SHINGLES)

Herpes zoster (shingles) is caused by varicella zoster virus (VZV) reactivation. It usually occurs in adults, but can be seen in children, especially if there has been a history of maternal varicella with in-utero infection of the child.

Antiviral treatment is indicated for:

- All patients seen within 72 hours of the onset of vesicles, especially patients over the age of 50 years. If > 72 hours of onset and new lesions are appearing, then treatment should be initiated as this indicates ongoing viral replication.
- All patients with ophthalmic herpes zoster. Refer to the chapter 'Infections of the eye' for further information regarding management of ophthalmic zoster.
- All patients with Ramsay Hunt syndrome (typically includes the triad of ipsilateral facial paralysis, ear pain, and vesicles in the auditory canal and auricle).
- All immunocompromised patients (e.g. HIV-infected patients) should be given antiviral therapy even if they present more than 72 hours after onset.

The goals of antiviral therapy are to promote more rapid healing of skin lesions, to decrease viral shedding, to lessen the severity and duration of pain associated with acute neuritis, and to reduce the incidence and severity of post-herpetic neuralgia.

TREATMENT: HERPES ZOSTER (SHINGLES)

UNCOMPLICATED ZOSTER

Acyclovir 800 mg PO 5 times per day

OR

Valacyclovir 1000 mg PO 8 hourly

Treat for 7 days

COMPLICATED INFECTION SUCH AS DISSEMINATED DISEASE

Adults: 10 mg/kg IVI 8 hourly

Treat for 10–14 days

PATIENTS WITH RAMSAY HUNT SYNDROME

Acyclovir 800 mg PO 5 times per day

OR

Valacyclovir 1000 mg PO 8 hourly

Treat for 7 days

Add prednisone 1 mg/kg for 5 days for all patients with Ramsay Hunt syndrome

In severe cases (e.g. vertigo, tinnitus, or hearing loss), IV therapy can be used initially and switched to an oral antiviral agent when the lesions begin to crust.

CYTOMEGALOVIRUS (CMV)

CMV INFECTION IN THE IMMUNOCOMPETENT HOST

Primary CMV infection in an immunocompetent host is generally asymptomatic or may present as a mononucleosis syndrome with fever and systemic symptoms. Primary infections in adults are rare however may result in a symptomatic mononucleosis-like illness with severe organ specific complications. CMV establishes a latent infection after resolution of the acute infection and may periodically reactivate. Infection of pregnant women, even if asymptomatic, may result in transmission to the foetus and subsequent congenital CMV in newborns. Antiviral therapy is not indicated for primary infections or reactivated infections in immunocompetent hosts unless there are severe organ specific complications.

CMV INFECTION IN THE IMMUNOCOMPROMISED HOST

CMV infection in immunocompromised patients can cause substantial morbidity and mortality, especially among transplant recipients and those infected with HIV. Most of the infections are secondary to reactivation of a latent infection. Important risk factors for CMV disease include: HIV-infected persons particularly when the CD4 count is less than 50 cells/μL, haematopoietic stem cell transplant recipients, highly immunosuppressive treatment regimens in solid organ transplant recipients, as well as CMV-seronegative transplant recipients receiving a seropositive graft.

CMV GASTROINTESTINAL DISEASE

CMV gastrointestinal disease can involve any part of the GI tract, most commonly the oesophagus (presenting with dysphagia or odynophagia), the colon (presenting with fever, weight loss, abdominal pain and diarrhoea), and less commonly the stomach and ileum. Maintenance suppressive therapy may be necessary in some patients with chronic severe immunosuppression to prevent relapse of CMV disease.

TREATMENT: CMV GASTROINTESTINAL DISEASE

Ganciclovir 5 mg/kg IV 12 hourly

Switch from IV to oral valganciclovir 900 mg 12 hourly when clinically improved and oral intake is tolerated

Treat for 14–21 days

MAINTENANCE SUPPRESSIVE THERAPY (PATIENTS WITH CHRONIC SEVERE IMMUNOSUPPRESSION, HIV-INFECTED PATIENTS UNTIL CD4 (> 100 CELLS/μL FOR ≥ 6 MONTHS)

Valganciclovir 900 mg PO once daily

CMV HEPATITIS

Subclinical transaminitis is frequently encountered in patients with symptomatic primary CMV infections. The benefit of antiviral therapy is not known. Symptomatic CMV hepatitis should however be treated as per gastrointestinal CMV disease recommendations.

NEUROLOGICAL MANIFESTATIONS INCLUDE ENCEPHALITIS AND VENTRICULITIS

Cytomegalovirus neurologic disease is an uncommon serious complication, typically seen in HIV-infected patients with CD4 counts < 50 cells/μL. Neurological disease is often rapidly fatal in these patients. Clinical presentations include encephalitis, myelitis, polyradiculopathy and peripheral neuropathy.

The diagnosis of CMV-related disease is based upon the clinical presentation, supported by findings on magnetic resonance imaging (MRI) or computerised tomography (CT), and/or documenting the presence of CMV infection in the cerebrospinal fluid by mean of a CMV PCR.

TREATMENT: CMV NEUROLOGICAL DISEASE

Ganciclovir 5 mg/kg IV 12 hourly

Treat for 14–21 days

MAINTENANCE SUPPRESSIVE THERAPY: HIV-INFECTED WITH CD4 <100 CELLS/μL

Valganciclovir 900 mg PO once daily

Continue until the patient is on ART and CD4 >100 cells/μL for ≥ 6 months

CMV PNEUMONITIS

CMV may cause pneumonia in organ transplant patients, typically lung transplant recipients, and rarely in HIV-infected patients with advanced disease (usually in those with a CD4 count < 20 cells/μL).

A laboratory diagnosis of CMV pneumonitis by means of positive lung biopsy histopathology and an elevated CMV viral load on a blood sample.

Note: CMV DNA is often detected by PCR in respiratory tract secretions in the absence of pulmonary disease. Detection of CMV in invasively obtained samples from the lower respiratory tract (e.g. BAL) is more specific for the diagnosis of CMV pneumonitis than upper tract samples however is often not diagnostic of CMV pneumonitis.

TREATMENT: CMV PNEUMONITIS

Ganciclovir 5 mg/kg IV 12 hourly

Treat for 14–21 days (until clinical resolution and negative blood CMV PCR)

Treatment with ganciclovir may be augmented by the addition of cytomegalovirus immune globulin, although there is limited data to support the efficacy of CMV immune globulin

MAINTENANCE SUPPRESSIVE THERAPY (PATIENTS AT HIGH RISK OF RELAPSE)

Valganciclovir 900 mg PO once daily for 1–3 months

CMV RETINITIS

Refer to the chapter ‘Eye Infections’ for further information.

CMV INFECTION DURING PREGNANCY

Primary CMV infection in pregnant women (very rarely CMV reactivation), even if asymptomatic, can result in congenital CMV infection. Approximately two percent of CMV IgG negative pregnant women will develop a primary CMV infection during pregnancy. CMV infection may cause a mild maternal febrile illness and other nonspecific symptoms but is asymptomatic in ~ 90% of women. The timing of primary maternal infection is the most important determinant of foetal sequelae. The risk of foetal infection increases with advancing gestational age at the time of maternal infection, but the occurrence of symptomatic disease in newborns decreases with advancing gestational age and is unlikely near term.

Congenital infection may be symptomatic or asymptomatic in neonates. Both symptomatic and asymptomatic infected newborns are at risk for developinging adverse sequelae in early childhood, but symptomatic newborns are at higher risk (e.g. death 5% vs. 0%, deafness 50% vs. 10%).

LABORATORY DIAGNOSIS: DURING PREGNANCY

Testing pregnant women for CMV is indicated as part of the diagnostic evaluation of women with mononucleosis-like illnesses or when a foetal anomaly consistent with congenital CMV infection is detected on prenatal ultrasound examination. The gold standard test for diagnosing suspected maternal primary CMV infection is based on CMV IgG seroconversion. In the absence of documented seroconversion, the presence of CMV IgG and CMV IgM may represent primary infection, reactivation, re-infection, or latent disease. In these cases, CMV IgG avidity testing is useful.

Prenatal (foetal) diagnosis may be offered when foetal infection is suspected because of primary maternal infection or findings on ultrasound. Testing includes amniocentesis and a CMV PCR on amniotic fluid after 21 weeks of gestation and at least six weeks after the presumed time of maternal infection. Although foetal infection can be detected by PCR, foetal prognosis is difficult to predict. An abnormal ultrasound examination suggests a poor prognosis, while a normal ultrasound examination does not exclude the possibility of a symptomatic neonate or subsequent development of long-term neurological morbidity.

LABORATORY DIAGNOSIS: AFTER PREGNANCY

Laboratory diagnosis of congenital CMV infection is accomplished by molecular detection of CMV DNA (PCR) from urine or saliva samples collected from the neonate within the first three weeks of life. Serology should not be used for the routine diagnosis of congenital CMV infection.

TREATMENT: CMV INFECTION IN PREGNANCY

During pregnancy, there is no treatment proven to be effective for preventing foetal disease or reducing the risk of sequelae. CMV hyperimmune globulin therapy of pregnant women with primary CMV infections in early pregnancy is a promising new approach to reduce the number of infants born with symptomatic disease. Women should be offered this therapy after discussion of the available data and potential risks.

TREATMENT: CONGENITAL CMV

Antiviral treatment is recommended for symptomatic infants with laboratory proven congenital CMV infection where it has been shown to improve long-term auditory and neurological outcomes. Treatment is also advised for asymptomatic infants with isolated hearing loss. Parenteral ganciclovir is recommended for infants with life-threatening disease and oral valganciclovir for those with non-life-threatening disease.

Patients started on ganciclovir can be switched to oral valganciclovir as soon as they are clinically stable and able to take oral medications (usually after two to six weeks). Treatment should be continued with valganciclovir for six months. CMV viral load monitoring on blood should be done,

and if the viraemia does not resolve after six months for severe symptomatic infants, antiviral therapy can be prolonged. Monitor patients on treatment for drug-induced toxicity (FBC, LFTs and renal function).

TREATMENT: CONGENITAL CMV

Life-threatening: Ganciclovir 6 mg/kg/dose IV 12 hourly (switch to oral valganciclovir after 2–6 weeks)

Non-life-threatening: Valganciclovir 16 mg/kg/dose PO 12 hourly

Treat for a minimum of 6 months

PARVOVIRUS B19

CLINICAL

Human parvovirus B19 infections are usually asymptomatic or mild and require only symptomatic treatment. Chronic parvovirus B19 infection can cause pure red cell aplasia in immunocompromised patients with certain leukaemias or cancers, recipients of organ transplants, patients with congenital immunodeficiencies and HIV-infected patients with advanced immunodeficiency. Since the anaemia is due to a pure red cell aplasia, peripheral reticulocytes are significantly reduced. Giant pronormoblasts are characteristically observed in the bone marrow. Intravenous immunoglobulin (IVIG), which contains a large amount of anti-parvovirus B19 IgG, is the treatment of choice for parvovirus B19 pure red cell aplasia.

TREATMENT: PARVOVIRUS

Intravenous immunoglobulin (IVIG) 400 mg/kg for 5–10 days

OR

Intravenous immunoglobulin (IVIG) 1000 mg/kg for 3 days

MAINTENANCE THERAPY: HIV PATIENTS WITH A CD4 < 100 CELLS/μL

Intravenous immunoglobulin (IVIG) 400 mg/kg once every 4 weeks

HEPATITIS B VIRUS

The following is intended to be a brief overview of the treatment of hepatitis B infections. For detailed information on the treatment of hepatitis B, please refer to the following guidelines:

Spearman CWN, Sonderup MW, Botha JF, Van der Merwe SW, Song E, Kassianides C, Newton KA, Hairwadzi HN. 2013. South African guideline for the management of chronic hepatitis B. *SAMJ* 103(5):335–349.

Terrault NA, Bzowej NH, Chang KM, Hwang JP, Jonas MM, Murad MH. 2016. AASLD guidelines for treatment of chronic hepatitis B. *Hepatology* 63(1):261–283.

ACUTE HEPATITIS B INFECTION

Most patients with acute hepatitis B infection generally do not require antiviral therapy and management is largely supportive. There is also no clear evidence that antiviral therapy for acute hepatitis B decreases the risk of chronicity or speeds up recovery. More than 90% of adults with acute hepatitis B will recover spontaneously and seroconvert to hepatitis B surface antibodies without therapy. The risk of liver failure with acute hepatitis B is less than one percent.

There are however certain patients that should receive antiviral treatment for acute hepatitis B:

- Those with fulminant hepatitis
- Those with a severe protracted acute hepatitis (INR ≥1.5; marked jaundice persisting > 4 weeks)

TREATMENT: ACUTE HEPATITIS B INFECTION

Treatment with tenofovir 300 mg PO daily or entecavir 0.5 mg daily is preferred

Dosage reduction is needed in patients with impaired renal function

Treatment can be stopped after confirmation that the patient is HBsAg ELISA negative (two consecutive tests four weeks apart)

CHRONIC HEPATITIS B INFECTION

Chronic hepatitis B (CHB) infection is defined as persistence of the hepatitis surface antigen (HBsAg) for longer than six months. The risk of developing chronic infection is dependent on the age and immune function of the patient at the time of the acute/initial infection:

- 90% of infected newborns progress to chronic infection
- 20–50% of children younger than five years progress to chronic infection
- < 5% of adults progress to chronic infection

Of those chronically infected, 15% to 40% may develop hepatitis B-related sequelae in their lifetime. Antiviral therapy can be given to prevent cirrhosis and hepatocellular carcinoma (HCC) from developing. If possible, it is recommended that patients with chronic hepatitis B be managed by a hepatologist or gastroenterologist.

PHASES OF CHRONIC HEPATITIS B

WHO	HBEAG	HBV DNA	ALT	HISTOLOGY	TREATMENT
Immune tolerant Usually children and young adults infected at birth	Positive	Elevated, typically > 1 million IU/mL	Normal	Minimal necroinflammation and fibrosis	Generally not indicated, monitor
Immune active (HBeAg positive CHB)	Positive	Elevated >20 000 IU/mL	Elevated	Moderate to severe necroinflammation	Usually indicated
Immune control (Inactive CHB)	Negative	Low or undetectable < 2000 IU/mL	Normal	Minimal necroinflammation but variable fibrosis	Generally not indicated, monitor
Immune reactivation (HBeAg negative CHB)	Negative	Elevated > 2000 IU/mL	Elevated	Moderate to severe necroinflammation	Usually indicated

SPECIAL INVESTIGATIONS

RECOMMENDED LABORATORY TESTING

- **Assessment of the severity of liver disease**
  - Liver function test. Note that the ALT upper limit of normal (ULN) is 30 U/L for males and 19 U/L for females.
  - FBC with differential count
  - Serum albumin and INR
- **Hepatitis B serology and replication**
  - Hepatitis B serology and hepatitis B viral load
- **Exclude other causes of liver disease/co-infections**
  - HIV serology
  - Hepatitis C serology
  - Hepatitis A serology: if negative, vaccinate
  - Alcoholic, autoimmune and metabolic liver disease

OTHER SPECIAL INVESTIGATIONS

LIVER BIOPSY

To evaluate the degree of fibrosis and necroinflammatory disease and can assist in the decision to start treatment. A biopsy is usually performed in patients older than 40 years, a family history of HCC and in patients with normal or mildly elevated ALT with an elevated viral load. A biopsy is usually not required in patients with evidence of cirrhosis, or in those in whom nucleoside analogue treatment is indicated.

SCREENING FOR HEPATOCELLULAR CARCINOMA

Perform as part of the initial investigations, if indicated.

TREATMENT OF CHRONIC HEPATITIS B

INDICATIONS FOR TREATMENT

A decision to treat is primarily based on the presence or absence of cirrhosis, the ALT level and the HBV viral load. There are additional indications for patients with certain concurrent conditions, such as immunocompromised patients and pregnant women.

TREATMENT: SHORT TERM GOALS

- Hepatitis B e antigen seroconversion
- Reduction of hepatitis B viral load to undetectable levels
- Normalisation of ALT levels

TREATMENT: LONG TERM GOALS

- Prevention of cirrhosis
- Prevention of decompensation and hepatocellular carcinoma in patients with cirrhosis

TREATMENT: ULTIMATE GOAL

- Loss of hepatitis B surface antigen with or without seroconversion to hepatitis B surface antibodies. This occurs in ~ 3% of patients on interferon based treatment and one to three percent of patients on one year of nucleoside/nucleotide analogue treatment.

CHRONIC HEPATITIS B TREATMENT RECOMMENDATIONS FOR NON-PREGNANT ADULTS*

PATIENTS WITHOUT CIRRHOSIS

HBEAG	HBV VIRAL LOAD	ALT	RECOMMENDED TREATMENT
Positive	> 20 000 IU/mL	≤ 2 x ULN	• Treatment generally not recommended. Consider if > 40 years or a family history of HCC • If not on treatment, monitor ALT every 3–6 months and treat if ALT > 2 ULN, or liver biopsy show moderate/severe inflammation or fibrosis • End-point of treatment: Loss of eAg
Positive	> 20 000 IU/mL	> 2 x ULN	• Treatment is indicated (if newly diagnosed, one can observe for 3–6 months for spontaneous eAg loss) • Treat with tenofovir or entecavir for at least 12 months after eAg seroconversion, OR PegINF-alpha for 48 weeks • End-point of treatment: Loss of eAg
Negative	> 2 000 IU/mL	> 2 x ULN OR 1–2 ULN with significant inflammation or fibrosis on liver biopsy	• Treatment is indicated • Treat with tenofovir or entecavir. Duration is several years or indefinite • Alternative treatment is PegINF-alpha for 12 months • End-point of treatment: Loss of sAg
Negative	≤ 2 000 IU/mL	≤ ULN	• Monitor ALT every 3–6 months and treat if ALT > 2 ULN, or liver biopsy show moderate/severe inflammation or fibrosis

PATIENTS WITH CIRRHOSIS

HBEAG	HBV VIRAL LOAD	ALT	RECOMMENDED TREATMENT
Positive or negative	Detectable	Any ALT	Compensated cirrhosis • Treat with tenofovir or entecavir
			Decompensated cirrhosis • Immediate treatment with entecavir (preferred) or tenofovir • Refer for liver transplant
Positive or negative	Undetectable	Any ALT	Compensated cirrhosis • Observe
			Decompensated cirrhosis • Refer for liver transplant

*Adapted from**:** Lok ASF. Hepatitis B virus: Overview of management. In: *UpToDate* Esteban R. (Ed.), *UpToDate* Waltham MA. (Accessed on March 08, 2017.)

ANTIVIRAL THERAPY

Treatment strategies typically include either pegylated interferon (PegIFN) or nucleoside/nucleotide analogues such as tenofovir and entecavir. The main advantage of interferon over the nucleoside/nucleotide analogues is the finite duration of treatment, absence of selection of drug resistant variants and a more durable treatment response. Interferon is often used for young patients who do not wish to be on long term treatment. However, side-effects, often severe, limit the use of interferon. Interferon is contraindicated in pregnant women, those with cirrhosis or decompensated disease, patients with portal hypertension, psychiatric disease, active autoimmune disease and significant cardiopulmonary disease.

DRUG	DOSE	COMMENTS
Pegylated interferon	Peginterferon alfa 2a 180 μg once weekly by subcutaneous injection	Predictors of a better response are eAg positive status, low HBV viral load and high ALT levels
Entecavir	0.5 mg PO daily (use 1 mg for decompensated disease)	• Do not use in patients previously treated with lamivudine due to cross-resistance. Rather use tenofovir • Dose adjust for renal impairment
Tenofovir disoproxil fumarate (TDF)	300 mg PO once daily	• Dose adjust for renal impairment • Can be used for those with prior drug exposure and drug resistance to other nucleoside/nucleotide analogues • Resistance to tenofovir has not been documented thus far
Tenofovir alafenamide (TAF) – if available)	25 mg PO once daily	TAF appears to be equally effective as TDF with less renal and bone toxicity

MONITORING OF PATIENTS ON HBV THERAPY*

INTERFERON TREATMENT	
INTERFERON: DURING TREATMENT	
Every 4 weeks	FBC and differential, INR, LFTs
Every 12 weeks	TSH, HBV viral load
Every 24 weeks	HBeAg, HBeAb (if initially eAg positive)
INTERFERON: AFTER TREATMENT	
Every 12 weeks for the first 24 weeks then every 6–12 months	FBC and differential, LFTs, TSH, HBV viral load, HBeAg, HBeAb (if initially eAg positive), HBsAg 6 monthly after HBe seroconversion, if HBV viral load undetectable.

NUCLEOSIDE/NUCLEOTIDE ANALOGUE TREATMENT	
Weeks 1 and 4	LFTs, serum creatinine and amylase, FBC and differential, INR
Every 12 weeks	LFTs, serum creatinine (if receiving tenofovir disoproxil fumarate or entecavir)
Every 12–24 weeks	HBV viral load
Every 24 weeks	HBeAg, HBeAb (if initially eAg positive)
Every 6–12 months	HBsAg in eAg positive patients after HBe seroconversion, HBsAg in eAg negative patients if HBV viral load undetectable

*Taken from: Spearman CWN, Sonderup MW, Botha JF, Van der Merwe SW, Song E, Kassianides C, Newton KA, Hairwadzi HN. 2013. South African guideline for the management of chronic hepatitis B. *SAMJ* 103(5):335–349.

SPECIAL PATIENT GROUPS

PREGNANT WOMEN WHO DO NOT HAVE ANY INDICATION TO START ANTIVIRAL THERAPY DURING PREGNANCY

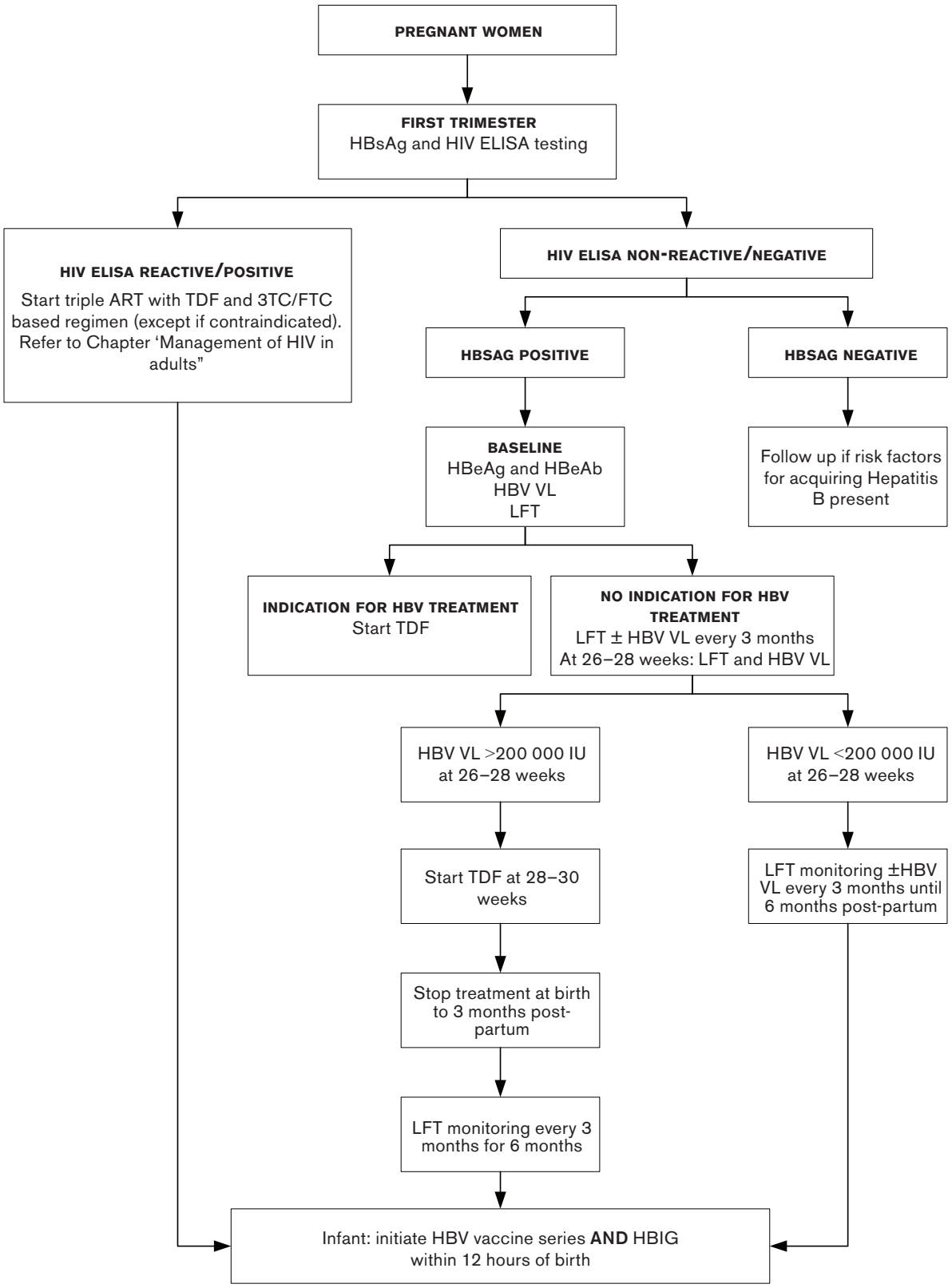
- Monitor for hepatic flares by doing liver function tests every three months during pregnancy and for six months postpartum.
- Perform HBV viral load at the same time or when there is ALT elevation.
- HBV viral load must be performed at 26–28 weeks gestation: if the HBV viral load is > 200 000 IU/mL then antiviral therapy should be started between 28 and 30 weeks gestation to reduce the risk of mother-to-child transmission even if the aminotransferase levels are normal.
  - Tenofovir disoproxil fumarate (TDF) should be used. Interferon is contraindicated.
  - Women who start antiviral therapy during pregnancy for the sole purpose of preventing mother-to-child transmission may stop antiviral therapy at birth to three months post-partum.
  - Women should be monitored for hepatic flares by liver function tests performed every three months for six months after treatment has been stopped.

PREGNANT WOMEN WITH INDICATIONS FOR ANTIVIRAL THERAPY

Indications for antiviral therapy in pregnant women are the generally the same as for non-pregnant women, but the following should be noted:

- Although antiviral therapy is recommended for most patients with an ALT > 2 x ULN, women without evidence of cirrhosis may choose to defer treatment until after delivery if they have low viral loads and mild disease activity.

HEPATITIS B IN PREGNANCY



PREGNANT WOMEN WITH HIV AND HEPATITIS B CO-INFECTION

Refer to the chapter 'Management of HIV infection in adults"

PATIENTS ON IMMUNOSUPPRESSIVE THERAPY

Antiviral therapy should be given to immune suppressed patients with chronic HBV, regardless of their ALT or viral load. Antiviral therapy must be started before the immunosuppressive therapy in initiated.

PATIENTS WITH HEPATOCELLULAR CARCINOMA

All patients with HCC should be treated with a nucleoside/nucleotide analogue.

PATIENTS WITH HEPATITIS C CO-INFECTION

These patients are at risk for HBV reactivation if they are stared on direct acting agents for their HCV infection. HBV treatment should be initiated prior to or at the same time as HCV therapy for those who meet the criteria for HBV treatment. For those that do not meet the criteria for HBV treatment, their HBV viral load should be monitored every four weeks and for up to 12 weeks after HCV therapy.

PATIENTS WITH HIV CO-INFECTION

Refer to the chapter 'Management of HIV infection in adults'.

SCREENING FOR HEPATOCELLULAR CARCINOMA

The aim of screening is to detect tumours early in order to offer curative therapy. HCC screening is performed with an ultrasound of the liver and serum alpha-fetoprotein every six to 12 months. Screening is indicated for the following patients:

- Africans older than 20 years
- Asian males $\geq$ 40 years and Asian females $\geq$ 50 years
- Caucasians with a high viral load and active inflammation: from 40 years for men and 50 years for women
- All patients with cirrhosis
- Those with a family history of HCC

HEPATITIS C VIRUS

The true prevalence of hepatitis C virus (HCV) is not known in South Africa, although existing data suggests a low overall prevalence. There are however pockets of at risk persons with high seroprevalence and large seroprevalence studies are underway to provide a clearer picture of the prevalence in higher risk populations. South Africa is a 'pan-genotype' country and is home to the unique genotype 5 (~ 40% of infections) with the remainder being genotypes 1–4.

The following is intended to be a brief overview of the treatment of hepatitis C infections. Developments in the field of HCV treatment are common and guidelines are changed frequently. For detailed information on the treatment of patients with hepatitis C, please refer to the following guidelines/publications:

- AASLD-IDSA. Recommendations for testing, managing, and treating hepatitis C. http://www.hcvguidelines.org.
- Burstow NJ, Mohamed Z, Gomaa AI, Sonderup MW, Cook NA, Waked I, Spearman CW, Taylor-Robinson SD. 2017. Hepatitis C treatment: where are we now? *International Journal of General Medicine* 10:39–52.

ACUTE HEPATITIS C INFECTION

Identification of acute HCV infections is not common as most acute infections are asymptomatic. Acute infections may be confirmed in patients who are symptomatic or when there has been laboratory monitoring for HCV infection following exposure to an infected source such as from a needlestick injury. HCV infection will spontaneously clear in 20% to 50% of patients and this largely occurs within six months of the estimated time of infection.

Interferon therapy given during the acute phase has been shown to significantly reduce the risk of developing a chronic infection by ~ 70%. Treatment should however be delayed for at least 12 weeks to allow for spontaneous resolution first. Oral direct-acting antiviral (DAA) regimens have not been extensively studied in acute infections although are expected to be highly effective and current international guidelines recommend the use of DAAs and the same regimes as for chronic infections.

THUS, THE CURRENT OPTIONS FOR TREATING ACUTE HEPATITIS C INFECTIONS ARE

- **Delayed treatment:** Monitor patients for spontaneous clearance for a minimum of six months. When the decision is made to initiate treatment after six months, treat as recommended for chronic hepatitis C.
- **Treatment during the acute infection:** Monitor HCV viral load for at least 12–16 weeks before starting treatment to allow for spontaneous clearance. If still viremic after 12–16 weeks then treat with either interferon therapy or a DAA regimen.

Cost and availability of DAAs is a major limiting factor for patients in South Africa and thus interferon-based therapy is likely to be used. For HIV-infected patients, ribavirin should be added to interferon treatment for acute HCV infections as the efficacy of interferon monotherapy for acute HCV is low in this group.

TREATMENT: ACUTE HEPATITIS C

Pegylated interferon alpha 2a 180 μg subcutaneously given weekly OR pegylated interferon alpha 2b 1.5 μg/kg subcutaneously given weekly

Standard interferon 5 MU subcutaneously daily for 4 weeks then 5 MU subcutaneously 3 times a week is an acceptable alternative

Add ribavirin 800 mg PO daily for all HIV co-infected patients

Duration of treatment is 24 weeks for genotype 1 and 12 weeks for the other genotypes

OR

Treat with a combination of direct-acting antiviral agents. Use the same drugs, dose and duration as recommended for chronic HCV infections

CHRONIC HEPATITIS C INFECTION

Patients with chronic hepatitis C should ideally be managed by an experienced hepatologist/gastroenterologist. New, highly effective direct acting agents are not yet registered by the MCC and drugs need to be sourced through early access programs or generic medications sourced from India and elsewhere. Hepatologists and gastroenterologists are familiar with local drug availability and how to access treatment for South African patients.

INDICATIONS FOR TREATMENT

All patients with virological evidence of chronic HCV (detectable HCV RNA over a six months period) should be considered for treatment.

GOALS OF TREATMENT

The goal of antiviral therapy is to eradicate HCV RNA from the patient. Eradication can be predicted by a sustained virological response (SVR) which is defined as an undetectable HCV viral load (limit of detection $\leq$ 15 IU/mL) three to six months after completing therapy. A SVR is associated with long-term clearance of HCV RNA in 97–100% of cases and thus defines a cure. Achieving a SVR reduces patient mortality, need for transplantation, prevents hepatocellular carcinoma, other liver- related complications and fibrosis.

WORKUP PRIOR TO STARTING HVC THERAPY

The initial assessment of patients diagnosed with chronic HCV includes:

- Assessment of the extent of liver disease, specifically identifying fibrosis or cirrhosis
- History of past antiviral use, current medication, drug and alcohol use
- Baseline HCV viral load and HCV genotype
- LFTs, serum albumin, FBC, renal function, INR
- HIV and HBV serology given common modes of transmission
- Assessment for extra-hepatic manifestations of chronic HCV such as cryoglobulinaema, porphyria cutanea tarda and autoimmune disorders

ANTIVIRAL DRUGS AND RECOMMENDED REGIMENS

INTERFERON AND RIBAVIRIN

Interferon therapy has been used to treat chronic hepatitis C since the early 1990s, together with oral ribavirin. Pegylated interferon and ribavirin have been standard of care in South Africa until the recent development of direct-acting antiviral agents. Response rates are genotype dependant with SVR rates around 40% for genotype 1 infections and up to 80% for genotypes 2, 3, 5 and 6. Patients experience significant side-effects and there are several contraindications to interferon therapy. Nowadays, interferon-free treatment regimens should be used where available.

DIRECT-ACTING ANTIVIRAL (DAA) THERAPY

It is useful to understand the structure of HCV and new direct-acting therapies target specific viral proteins. The RNA viral genome encodes a polyprotein which is cleaved into four structural and six non-structural (NS) proteins.

The non-structural proteins NS3/4A, NS5A and NS5B proteins are the current important antiviral drug targets:

- **NS3/4A inhibitors:** telaprevir, boceprevir, simeprevir, grazoprevir, paritaprevir, asunaprevir, voxileprevir, glecaprevir
- **NS5A inhibitors:** daclatasvir, ledipasvir, elbasvir, ombitasvir, velpatasvir, odalasvir
- **NS5B inhibitors:** sofosbuvir, dasabuvir

The introduction of these direct-acting antiviral agents has revolutionised therapy. Highly effective, well-tolerated, interferon-free (and in most cases ribavirin-free) regimens are the choice of therapy for those that can afford and have access to them.

As yet, no direct-acting antiviral agents are currently licensed in South Africa (March 2017) and thus DAAs need to be accessed via either two routes:

- Though Gilead's 'International Access' program. Pricing is different for public and private sectors. Solvadi® (sofosbuvir/ledipasvir) and Harvoni® (sofosbuvir/daclatasvir) are priced at US$300 and US$400 per bottle, respectively, in the public sector and US$2700 and US$3500 per bottle, respectively, for the private sector. These need to be accessed via a section 21 application, on a names patient basis, to the MCC.

- Purchasing generic DAAs. Several generic DAAs are being manufactured under licence from the originator companies, by pharmaceutical companies in India, Egypt and elsewhere. This has resulted in relatively inexpensive, generic products of sofosbuvir/ledipasvir and sofosbuvir/daclatasvir being available for countries to access. This is currently the preferred route to access DAAs for patients in South Africa. Registration of DAAs is expected to happen in South Africa, and when this happens it will become illegal to use unregistered international generic drugs. Local prices are likely to be more than international generics and this is going to pose a problem to those self-funding treatment.

RECOMMENDED TREATMENT REGIMENS*

The current interferon-free regimes recommended by the AASLD and EASL are as follows:

PATIENTS WITHOUT CIRRHOSIS

GENOTYPE	TREATMENT NAIVE	TREATMENT EXPERIENCED
1	SOF/LDV (8–12 weeks) SOF/VEL (12 weeks) RTV-PTV/OBV/DSV ± RBV (8–12 weeks)[b] GZR/EBR (12 weeks)[c] SOF + DCV (12 weeks) SOF + SMV (12 weeks)	SOF/LDV ± RBV (12 weeks)[a] SOF/VEL (12 weeks) RTV-PTV/OBV/DSV ± RBV (12 weeks)[b] GZR/EBR (12 weeks)[c] SOF + DCV ± RBV (12 weeks)[a] SOF + SMV (12 weeks)
2	SOF/VEL (12 weeks) SOF + DCV (12 weeks)	SOF/VEL (12 weeks) SOF + DCV (12 weeks)
3	SOF/VEL (12 weeks) SOF + DCV (12 weeks)	SOF/VEL ± RBV (12 weeks)[d] SOF + DCV ± RBV (12 weeks)[d]
4	SOF/LDV (12 weeks) SOF/VEL (12 weeks) RTV-PTV/OBV + RBV (12 weeks) GZR/EBR (12 weeks) SOF + DCV (12 weeks) SOF + SMV (12 weeks)	SOF/LDV ± RBV (12 weeks)[d] SOF/VEL (12 weeks) RTV-PTV/OBV + RBV (12 weeks) GZR/EBR (12 weeks)[e] SOF + DCV ± RBV (12 weeks)[d] SOF + SMV ± RBV (12 weeks)[d]
5/6	SOF/LDV (12 weeks) SOF/VEL (12 weeks) SOF + DCV (12 weeks)	SOF/LDV ± RBV (12 weeks)[d] SOF/VEL (12 weeks) SOF + DCV ± RBV (12 weeks)[d]

PATIENTS WITH CIRRHOSIS

GENOTYPE	COMPENSATED: NAIVE OR EXPERIENCED	DECOMPENSATED
1	SOF/LDV ± RBV (12 weeks)[f] SOF/VEL (12 weeks) RTV-PTV/OBV/DSV ± RBV (12/24 weeks)[g] GZR/EBR (12 weeks)[h] SOF + DCV ± RBV (12 weeks)[f] SOF + SMV (12 weeks)	SOF/LDV + RBV (12 weeks)[l] SOF/VEL + RBV (12 weeks)[l] SOF + DCV + RBV (12 weeks)[l]
2	SOF/VEL (12 weeks) SOF + DCV (12 weeks)	SOF/VEL + RBV (12 weeks)[l] SOF + DCV + RBV (12 weeks)[l]
3	SOF/VEL (12 weeks)[i] SOF + DCV + RBV (24 weeks)	SOF/VEL + RBV (24 weeks)[l] SOF + DCV + RBV (24 weeks)[l]
4	SOF/LDV ± RBV (12 weeks)[j] SOF/VEL (12 weeks) RTV-PTV/OBV + RBV (12 weeks) GZR/EBR (12 weeks)[k] SOF + DCV ± RBV (12 weeks)[j] SOF + SMV ± RBV (12 weeks)[j]	SOF/LDV + RBV (12 WEEKS)[L] SOF/VEL + RBV (12 WEEKS)[l] SOF + DCV + RBV (12 WEEKS)
5/6	SOF/LDV ± RBV (12 weeks)[j] SOF/VEL (12 weeks) SOF + DCV ± RBV (12 weeks)[j]	SOF/LDV + RBV (12 weeks)[l] SOF/VEL + RBV (12 weeks)[l] SOF + DCV + RBV (12 weeks)[l]

NOTES

a. If GT1a, add RBV or extend to 24 weeks without RBV.
b. If GT1a, add RBV and treat for 12 weeks.
c. If GT1a with viral load > 800,000 IU/mL, extend to 16 weeks plus RBV.
d. Treat for 12 weeks with RBV or 24 weeks without RBV.
e. If viral load > 800,000 IU/mL, extend to 16 weeks plus RBV.
f. If GT1a treatment-experienced, give 12 weeks with RBV or 24 weeks without.
g. If GT1a, 24 weeks with RBV. If GT1b, 12 weeks without RBV.
h. If GT1a with viral load > 800,000 IU/mL, extend to 16 weeks plus RBV.
i. If resistance-associated mutations, give 12 weeks with RBV or 24 weeks without.
j. If treatment-experienced, give 12 weeks with RBV or 24 weeks without.
k. If treatment-experienced with viral load > 800,000 IU/mL, extend to 16 weeks plus RBV.
l. If intolerant to RBV, give 24-week therapy without RBV.

Abbreviations: AASLD, American Association for the Study of Liver Diseases; EASL, European Association for the Study of the Liver; SOF, sofosbuvir; LDV, ledipasvir; RBV, ribavirin; VEL, velpatasvir; RTV, ritonavir; PTV, paritaprevir; OBV, ombitasvir; DSV, dasabuvir; GZR, grazoprevir; EBR, elbasvir; DCV, daclatasvir; SMV, simeprevir; GT, genotype.

*Taken from: Burstow NJ, Mohamed Z, Gomaa AI, Sonderup MW, Cook NA, Waked I, Spearman CW, Taylor-Robinson SD. 2017. Hepatitis C treatment: where are we now? *International Journal of General Medicine* 10:39–52.

MONITORING OF PATIENTS ON/FOLLOWING HCV TREATMENT WITH INTERFERON-FREE REGIMENS

Adherence counselling is essential and should be provided at each visit and any side-effects should be discussed and managed. Side effects on DAAs are however rare.

The AASLD recommends the following routine laboratory tests for patients treated with DAAs:

- Week 4 of treatment: FBC, U&E, LFTs and HCV viral load
- Week 6 of treatment: HCV viral load (only if the week 4 viral load was detectable)
- 12 weeks after the end of treatment: HCV viral load. A sustained virological response is defined by an undetectable viral load at this point and this defines a cure.
- If ribavirin is used in a regimen then check the FBC at weeks four, eight and 12 and check for anaemia. Dose adjustment may be indicated for patients with anaemia.
- For patients receiving elbasvir-grazoprevir, check LFTs at week eight (and week 12, if treatment duration is 16 weeks).
- For patients with cirrhosis receiving paritaprevir-ritonavir-ombitasvir-based regimens, monitor for decompensation and perform LFTs at week 2, 4, 12 and 24.

FOR PATIENTS THAT ACHIEVE A SUSTAINED VIROLOGICAL RESPONSE

- If no cirrhosis or bridging fibrosis, then no specific follow up indicated. A repeat HCV viral load one year after completing treatment is advised to ensure maintenance of SVR.
- A SVR does not confer immunity to HCV and thus patients need to be counselled that they are at risk of re-infection with future exposures.
- Patients with advanced fibrosis or cirrhosis require ongoing monitoring for hepatocellular carcinoma and other complications.

FOR PATIENTS THAT DO NOT ACHIEVE A SUSTAINED VIROLOGICAL RESPONSE

- Monitor signs of progression of liver disease and assess for re-treatment.
- Patients with advanced fibrosis or cirrhosis require ongoing monitoring for hepatocellular carcinoma and other complications.

INFLUENZA

Influenza infection in humans is caused by influenza A and influenza B viruses. The laboratory test of choice is an influenza PCR performed on a respiratory tract specimen such as a throat swab or nasopharyngeal aspirate. Rapid antigen tests lack sensitivity and their use is not recommended.

INFLUENZA POST-EXPOSURE PROPHYLAXIS

Refer to the chapter 'Pre-exposure and post-exposure prophylaxis' for further information.

INFLUENZA TREATMENT

Treatment should be given to the following patients with suspected or laboratory confirmed infections:

Patients who are at high risk for influenza complications regardless of disease severity

- Children younger than two years
- Adults 65 years and older
- Persons (adults or children) with chronic underlying medical conditions and who are receiving regular medical care for conditions such as chronic pulmonary disease (including asthma) and cardiac disease (excluding hypertension), chronic renal and hepatic diseases and diabetes mellitus.

- Individuals who are immunosuppressed (including HIV-infected persons, and persons on immunosuppressive medications).
- Adults and children who have any condition (e.g. cognitive dysfunction, spinal cord injuries, seizure disorders, or other neuromuscular disorders) that can compromise respiratory function or the handling of respiratory secretions or that can increase the risk for aspiration.
- Morbid obesity (BMI > 30) as this has been identified as a risk factor for complications of H1N1 influenza as well as pulmonary embolic disease.
- Children and adolescents who are receiving long-term aspirin therapy and who might be at risk for experiencing Reye's syndrome after influenza virus infection.
- Residents of nursing homes and other chronic-care facilities.
- Pregnant women and those postpartum (with two weeks of delivery).

PATIENTS WHO HAVE MODERATE TO SEVERE DISEASE, COMPLICATED OR PROGRESSIVE ILLNESS

- Influenza requiring hospital admission and/or with symptoms and signs of lower respiratory tract infection (hypoxaemia, dyspnoea, lung infiltrate), central nervous system involvement and/or a significant exacerbation of an underlying medical condition.

When indicated, antiviral therapy should be initiated as soon as possible since antiviral therapy is most likely to provide benefit when initiated within the first 48 hours of the illness. Treatment should not be delayed while awaiting laboratory results nor should it be withheld in patients with indications for therapy who present after 48 hours of the onset of symptoms, particularly for patients that require hospitalisation.

Recommended treatment duration is five days. For patients with severe infections and immune compromised patients, longer courses of treatment up to 10 days can be used. Higher doses have not been shown to be more efficacious in patients who are severely ill; rather extend the duration of treatment to seven to ten days. Standard doses should be used in obese patients as they achieve adequate therapeutic levels of the active drug. Corticosteroids are not advised for severely ill patients and the evidence thus far points to a possible increase in mortality where steroids are added to antiviral therapy.

℞ **RECOMMENDED DOSES OF NEURAMINIDASE INHIBITORS FOR INFLUENZA A AND B INFECTIONS**

	OSELTAMIVIR (TAMIFLU®)	ZANAMIVIR (RELENZA®)
ADULTS		
	75 mg PO 12 hourly	Two 5 mg inhalations (10 mg total) twice per day
CHILDREN		
15 kg or less	30 mg PO 12 hourly	Two 5 mg inhalations (10 mg total) twice per day (only in children aged 7 years or older)
15–23 kg	45 mg PO 12 hourly	
24–40 kg	60 mg PO 12 hourly	
> 40 kg	75 mg PO 12 hourly	

NEONATES AND INFANTS		
Premature neonates/infants 28–37 weeks postmenstrual age	1 mg/kg PO 12 hourly	Cannot be given
Premature neonates/infants 38–40 weeks postmenstrual age	1.5 mg/kg PO 12 hourly	
Premature neonates/infants > 40 weeks postmenstrual age	3 mg/kg PO 12 hourly	
Full term neonates and infants (1 day to 9 months)	3 mg/kg PO 12 hourly	
Full term infants (9–12 months)	3.5 mg/kg PO 12 hourly	

HUMAN PAPILLOMAVIRUS INFECTION

Human papillomaviruses (HPVs) infect the epithelium of skin and mucous membranes, and clinically present with:

- Anogenital disease: genital warts (condylomata acuminata), and cancer of the cervix, anus, vulva, penis and vagina
- Cutaneous disease: common, plantar and flat warts
- Other rare mucous membrane manifestations such as recurrent respiratory papillomatosis

CERVICAL INFECTION BY HPV IN WOMEN

HPV is the most common sexually transmitted infection today, and persistent infection with high-risk genotypes is the cause of cervical cancer. Most genital HPV infections are transient and asymptomatic. Approximately 70% of women with genital infections become HPV DNA negative within one year, and approximately 91% within two years following the initial infection.

HPV GENOTYPES CAN BE DIVIDED INTO "HIGH-RISK" AND "LOW-RISK" TYPES:

HIGH-RISK TYPES: ONCOGENIC OR CANCER-ASSOCIATED	LOW-RISK TYPES: NON-ONCOGENIC
16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 82	6, 11, 40, 42, 43, 44, 54, 61, 72, 73, 81
Persisting infections with high-risk HPV (hr-HPV) genotypes lead to precancerous lesions and ultimately cervical cancer. Approximate contribution of genotypes in causing cervical cancer: • HPV-16: ± 60% • HPV-18: ± 10%, • HPV-31: ± 4% • HPV-45: ± 4% • HPV-33, 52 and 58 together: ± 2%	These HPV genotypes cause benign or low-grade lesions and genital warts.

TERMINOLOGY

TERM	DESCRIPTION
Cervical cancer screening	Testing asymptomatic women in order to detect cervical dysplasia by using cytology and/or hr-HPV DNA testing.
Triage test	A test that is applied to those with a positive screening test to identify women who require colposcopy.
HPV co-testing	The simultaneous use of both cytology and HPV testing. Although still recommended in the USA it is not widely used elsewhere as it is more costly and has virtually no added value compared to hr-HPV DNA screening alone in women 30–65 years of age.
ASC-US	Atypical squamous cells of undetermined significance.
LSIL	Low-grade squamous intraepithelial lesion encompassing HPV/mild dysplasia/CIN1.
ASC-H	Atypical squamous cells – cannot exclude HSIL.
HSIL	High-grade squamous intraepithelial lesion encompassing: moderate and severe dysplasia, CIN2, CIN3, and carcinoma in situ.

LABORATORY TESTING

MOLECULAR TESTS FOR HPV

TEST	DESCRIPTION	ROLE AND SPECIMEN
High risk HPV DNA PCR	Detects the presence of DNA for the following 14 high-risk HPV genotypes: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68 Provides partial genotyping: • HPV 16 • HPV 18 • Other high-risk HPV genotypes (without identifying the specific genotypes)	Role: cervical screening Specimen: liquid-based cytology (LBC) specimen which can be used for both hr-HPV DNA and cytology as needed
Full HPV DNA genotyping PCR	Identifies the presence of a number of high, intermediate and low-risk HPV genotypes and determines the specific genotype present. Can identify the following genotypes: 6, 11, 16, 18, 26, 31, 33, 35, 39, 40, 42, 45, 51, 52, 53, 54, 55,56, 58, 59, 61, 62, 64, 66, 67, 68, 69, 70, 71, 72, 73, 81, 82, 83 , 84.	Role: used for cutaneous, oral and genital papillomas Available on specific request Specimen: LBC or tissue

HPV mRNA (messenger RNA)	Detect mRNA from the viral oncogenes E6/E7 which implies that the virus has integrated into the host and is disrupting the cell cycle control.	Not offered by Ampath

ADVANTAGES OF PRIMARY HR-HPV DNA SCREENING COMPARED TO CYTOLOGY

- ± 30% more sensitive in detecting CIN2+ lesions compared to cytology
- ± 20% more sensitive in detecting CIN3+ lesions compared to cytology
- Provides 60–70% greater protection against invasive cervical cancer compared to cytology-based screening
- Allows an extension of the screening intervals to five years compared to the recommended three yearly intervals for cytology if hr-HPV DNA negative

LIMITATIONS OF HR-HPV DNA SCREENING

- HPV DNA assays, whilst highly sensitive for detecting HPV infections, are not able to distinguish an infection that will clear spontaneously from one that will become persistent and lead to precancerous lesions and ultimately cervical cancer (i.e. specificity is poor). For this reason women who test hr-HPV DNA positive require what is known as a 'triage test' to determine which of them has an underlying precancerous lesion that requires treatment.

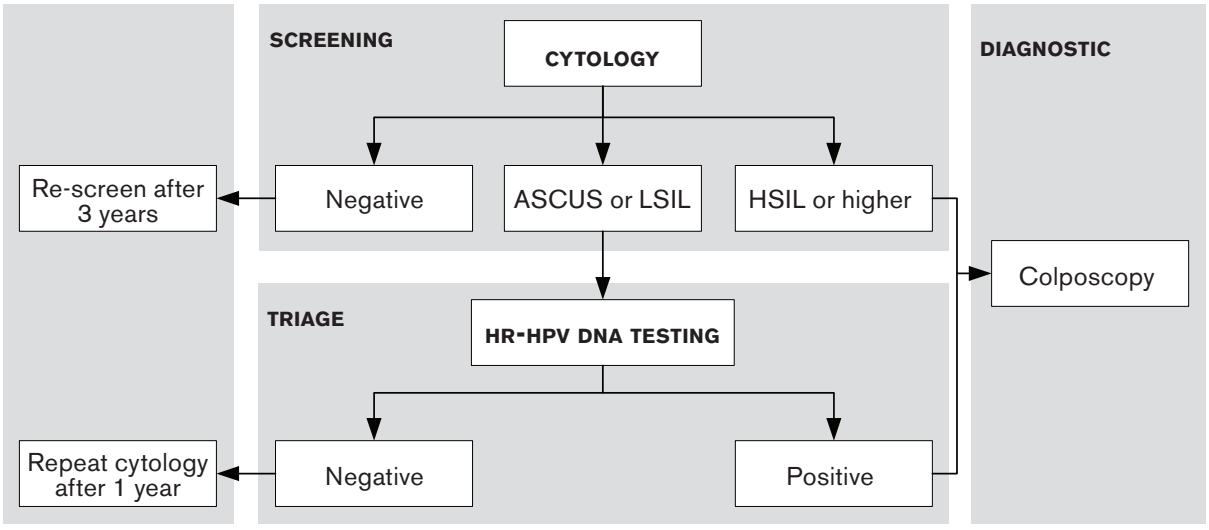
HR-HPV DNA TESTING AND GENOTYPING IS NOT RECOMMENDED FOR THE FOLLOWING PATIENTS

- Routine screening in women before the age of 30 years as HPV infections are common and usually transient
- Testing male partners of patients with genital warts, cervical dysplasia or cancer
- Testing male partners of women positive for high-risk HPV
- Testing male patients
  - There is no approved test to detect HPV in men
  - There is no effective and reliable way to collect a specimen of male genital skin cells
  - It is unclear which part of the male genitalia should be tested for HPV
  - It is unclear how a positive test result in male patients should be interpreted

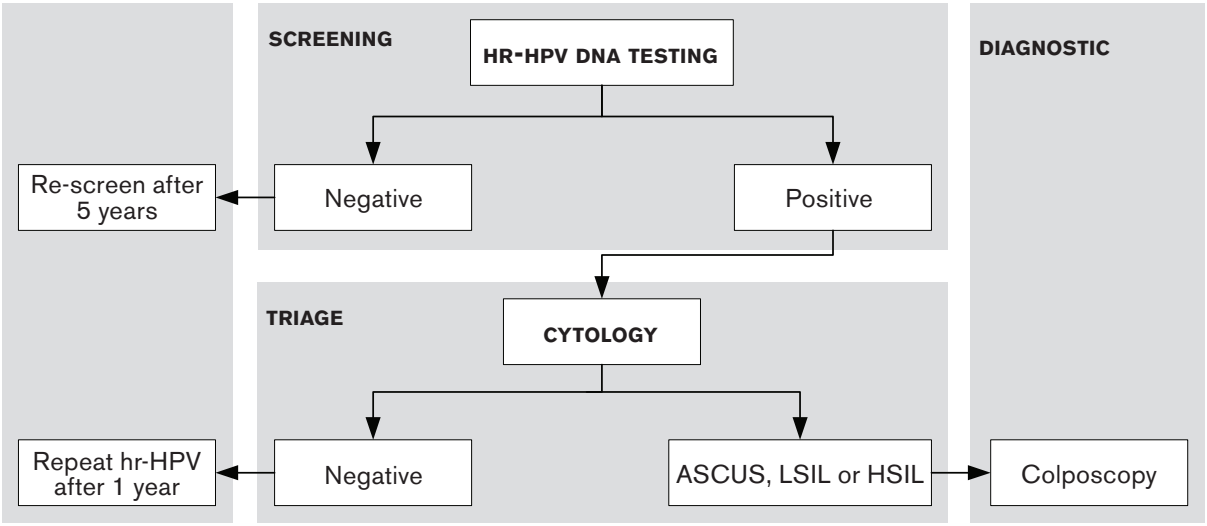
RECOMMENDED TESTS FOR CERVICAL CANCER SCREENING PER AGE GROUP

AGE (IN YEARS)	SCREENING METHOD	COMMENTS
21–30	Cytology	Do not use hr-HPV DNA screening due to higher rates of HPV infection and transient nature of these infections. Re-screen after 3 years if cytology negative.
30–65	hr-HPV DNA	Primary hr-HPV DNA screening can be used as an alternative to cytology based screening programmes in women 30–65 years of age. Cytology should be used to triage hr-HPV DNA positive women to determine the need for colposcopy. Re-screen after 5 years if hr-HPV DNA negative.
Older than 65	Stop screening	Stop only if there is no prior history of CIN and the last hr-HPV DNA test was negative.
HIV-infected women (any age)	Cytology annually	Utility of hr-HPV DNA screening has not been determined.

WOMEN 21–30 YEARS OF AGE: SCREENING AND MANAGEMENT



WOMEN 30–65 YEARS OF AGE: SCREENING AND MANAGEMENT



WARTS

TREATMENT OPTIONS FOR CUTANEOUS WARTS

- Spontaneous regression occurs in as many as two-thirds of warts within two years, and therefore observation is an option in all patients.
- Treat filiform warts with 'snip or shave excision' with scissors or a scalpel blade.
- In children old enough to comply with therapy, treat common, plantar and palmar warts with 15% salicylic acid ointment covered with Elastoplast with removal of dead skin with a nail file or pumice stone between treatments.
- In adults with common, plantar or palmar warts, treat with liquid nitrogen or 15% salicylic acid covered with Elastoplast with removal of dead skin with a pumice stone or corn blade.
- For flat warts, 5-fluorouracil (Efudex® 5% cream) applied to affected skin twice daily for three to five weeks, or imiquimod (Aldara®) applied three times per weeks at bedtime can be used.
- Where scarring is a concern (e.g. facial lesions), treat with topical imiquimod (Aldara®).

TREATMENT OPTIONS FOR ANOGENITAL WARTS

- For external anogenital warts, podophyllotoxin 0.5% paint (Wartec®) topically applied to the wart, twice daily for three days followed by a four day break – repeat weekly for four to six cycles until the warts disappear.
- Imiquimod (Aldara®) applied three times per week at bedtime and washed off in the morning is an alternative treatment option for anogenital warts.
- Ablative or excisional surgical therapy may be required for large warts, as often seen in the anogenital region, or when medical treatment has failed.

RESPIRATORY SYNCYTIAL VIRUS

Respiratory syncytial virus (RSV) causes acute respiratory tract illness in persons of all ages, especially in children under two years of age. Treatment of RSV infection of the lower respiratory tract is primarily supportive. Ribavirin is a nucleoside analogue with good in vitro activity against RSV and may be used either orally or via aerosolisation in certain high-risk patients with lower respiratory tract infections (LRTI).

RIBAVIRIN USE IN YOUNG CHILDREN

The routine use of aerosolised ribavirin in infants and children with RSV lower respiratory tract infection is not recommended. Ribavirin should be reserved for immunosuppressed patients with severe RSV infection and consultation with an expert in infectious diseases is recommended before using ribavirin.

Inhaled bronchodilators should not be used routinely for children with RSV bronchiolitis, nor corticosteroids in infants and young children (< 24 months) with RSV bronchiolitis or pneumonia.

RIBAVIRIN USE IN ADULTS

Early use of aerosolised ribavirin has been shown to reduce morbidity and mortality in adult hematopoietic cell transplant recipients with RSV infections. Oral ribavirin is an alternative and in a small case series, oral ribavirin (dose 15–20 mg/kg/day dosed eight hourly for seven to 10 days) has been used to successfully treat RSV upper and lower respiratory tract disease in adult hematopoietic cell transplant recipients. The efficacy of ribavirin for patients with solid-organ transplants is not known. Corticosteroids may be beneficial in immunocompromised adults with severe RSV LRTI as well as for the management of lower airway obstruction in older children and adults.

RIBAVIRIN AEROSOLISATION OPTIONS

DOSING STRATEGY	TOTAL DAILY DOSE	DOSE AND INTERVAL	RIBAVIRIN CONCENTRATION
Standard dosing/FDA-approved	6 g	6 g nebulised continuously for 12–18 hours	20 mg/mL
High dose, short duration	6 g	2 g nebulised over 2 hours, given 8 hourly	60 mg/mL
Alternative	6 g	6 g nebulised continuously for 6 hours	60 mg/mL

Aerosolisation of ribavirin should be performed using a Small Particle Aerosol Generator (SPAG). The SPAG is designed to produce particles of appropriate size for deposition in appropriate lung areas for the treatment of RSV infections. The SPAG can be connected to a facemask, an aerosol tent, or a ventilator. Special care should be used when attaching the SPAG to a mechanical ventilator to prevent drug precipitation and increased pulmonary pressures, including use of heated-wire connective tubing and frequent suctioning and tubing changes (2–4 hours).

Aerosolisation of ribavirin in children involves 12–18 hours of continuous aerosol delivery. Recent studies using aerosolised ribavirin in adults have used high-dose, short-duration regimens that differ from the FDA-approved dosing and may be more practical for nursing care.