

SECTION 9

ADVANCED HIV DISEASE (AHD)

This section provides information about advanced HIV disease (AHD). What is AHD, what are the warning signs, and how can it be prevented? What do people with AHD need?

After reading this section, you will have a basic understanding of:

- » The definition of AHD
- » The warning signs of AHD
- » How to prevent AHD
- » The package of treatment and care for AHD
 - Illnesses that people with AHD are at risk of (called opportunistic infections)
 - Testing for and prevention and treatment of opportunistic infections



DEFINITION OF ADVANCED HIV DISEASE (AHD)

AHD means you have or could get certain illnesses that happen when someone has a low CD4 cell count.

CD4 cells are infection-fighting white blood cells that work with other parts of your immune system to keep you healthy. A normal CD4 count ranges from 500 to 1,600 cells/mm³.

In adults and adolescents (including those who are pregnant) and children over five years old (living with HIV), AHD means having a CD4 cell count less than 200 cells/mm³ or the occurrence of certain opportunistic infections. All children under age five have AHD.

The risk of dying is higher with a low CD4 count, especially if it is less than 100 cells/mm³.

Severe AHD is a CD4 cell count of less than 50 cells/mm³.



CD4 CELLS AND HIV

Your body makes CD4 cells to fight off HIV – and other infections. When it is untreated, HIV causes CD4 cells to self-destruct – or to be killed by other parts of the immune system. Over time, as more CD4 cells die, a person's immune system becomes weak. The fewer CD4 cells you have, the more you are at risk of illness.

In South Africa, almost a third of people living with HIV start treatment, called antiretroviral therapy (ART), with a low CD4 cell count.

DANGER SIGNS OF AHD

Some people with AHD will not feel ill, but others will become seriously ill.

For adults and adolescents, the danger signs include:

- » Rapid breathing
- » Rapid heart rate
- » Not being able to walk without help
- » High fever (39°C or higher)

For children, the danger signs include:

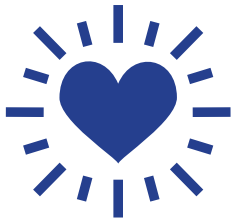
- » Tiredness
- » Becoming unconscious
- » Unable to drink or breastfeed
- » Repeated vomiting
- » Convulsions (sudden, violent, irregular movements)
- » High fever (39°C or higher)

The presence of one or more of these danger signs requires an immediate visit to the hospital.

PREVENTING AHD

The best way to prevent AHD is to start ART when your CD4 count is high.

Everyone should start ART when they are diagnosed with HIV, whatever their CD4 count.



TREATMENT AND CARE FOR AHD

Everyone who is diagnosed with HIV or re-entering care should get a CD4 test.

It is important for people with AHD to get the information and support they need, so that they feel ready to start ART as soon as possible. Even on the same day as their HIV diagnosis. Starting ART – or re-starting it – right away gives people with AHD the best chance of getting better and avoiding illnesses, even with a very low CD4 count.*

The most important thing that people living with HIV can do to stay healthy is to take ART at the same time each day, with or without food (as advised) and not miss doses.

People with AHD should receive special care and treatment, including counselling and adherence support, ART, tests for other infections and medicines to prevent or treat them. If needed, people with AHD should be offered home visits and help with getting to clinic appointments.

**In some cases, people with AHD may need to delay ART until they begin treatment for other infections (tuberculosis and cryptococcal meningitis).*

OPPORTUNISTIC INFECTIONS

People with AHD are at risk for certain infections that occur when the immune system is weakened, called opportunistic infections (OI). The most common among people with AHD are:

- » Tuberculosis (TB)
- » Serious Bacterial Infections
- » Cryptococcal Meningitis
- » Pneumocystis Jirovecii Pneumonia (PCP)
- » Toxoplasmosis
- » Cytomegalovirus (CMV)



TUBERCULOSIS (TB)

What is it, and what causes it?

Tuberculosis (TB) is an airborne bacterial infection that can occur in every part of the body except the hair and nails. Usually, TB infects the lungs; this is called pulmonary TB. TB outside the lungs is called extrapulmonary TB.

TB spreads when someone with untreated TB coughs, sneezes, sings or spits, sending tiny droplets of TB bacteria into the air which other people inhale. People with a strong immune system may never become ill from TB, although they are infected; this is called latent TB infection (LTBI). When the immune system is weak, people with LTBI are far more likely to fall ill from TB – called active TB.

All people living with HIV are at risk for TB, especially people with AHD, who are more likely to have extrapulmonary TB. ART lowers the risk for TB, especially when it is used with TB preventive treatment.

TB is the leading cause of death among people living with HIV, but it is preventable, and usually curable although some forms of it are more difficult to treat due to drug resistance.

What are the symptoms of pulmonary TB?

Primary symptoms of pulmonary TB:

- » Cough
- » Weight loss
- » Fever
- » Night sweats

Other symptoms include:

- » A cough that does not go away
- » Coughing up blood
- » Chest pain
- » Weakness

Note that children may have atypical symptoms in pulmonary TB – like not growing or gaining weight as expected (failure to thrive).

What are the symptoms of extrapulmonary TB?

- » Fever
- » Fatigue
- » Weight loss
- » Other symptoms vary, depending on which part of the body has become infected with TB.

Table 1: Summary of care for TB in AHD

	ADULTS (age greater than 19 years) <i>(including during pregnancy)</i>	ADOLESCENTS (age from 10-19 years)	CHILDREN (age less than 10 years)	INFANTS (age less than 1 year)
TESTING for PULMONARY TB (testing for extrapulmonary TB varies depending on where it is in the body)	<p>Active TB testing with Xpert MTB-RIF (which uses a sample of sputum) is recommended for all people with AHD who have TB symptoms, regardless of age. People who are diagnosed with TB may need more tests for TB drug resistance.</p>			
	<p>TB-LAM testing (which uses a urine sample) is recommended for all hospitalized adults, adolescents and children who are less than 5 years old with AHD and TB symptoms and/or are seriously ill. TB-LAM testing is also recommended for all outpatient adults, adolescents and children who are less than 5 years old with a CD4 count of less than 100 cells/mm³ and /or those who are seriously ill.</p>		<p>TB-LAM testing is recommended for all infants and children who are less than 5 years old with TB symptoms.</p>	
PREVENTION	<p>Preventive treatment is recommended for all adults and adolescents living with HIV, regardless of CD4 count, who are unlikely to have active TB; this includes pregnant women and people who have successfully completed TB treatment – and even when LTBI testing is unavailable.</p> <p>Examples of TB preventive therapy (TPT): Isoniazid given daily for 6 to 9 months has been the most widely used TB preventive treatment (TPT) regimen worldwide. Rifampicin can be given alone for 4 months ("4R") or with isoniazid for 3 months ("3HR"). Rifapentine can be given together with isoniazid in a weekly dose for three months ("3HP") or daily for one month ("1HP").</p>		<p>All children unlikely to have active TB should be offered TB preventive treatment if they are in areas with a high rate of TB transmission; this includes children who have successfully completed TB treatment.</p>	<p>In South Africa, the Bacille Calmette-Guérin (BCG) vaccine is given at birth to protect against TB (except to infants with symptoms of HIV or who are very ill). WHO recommends BCG vaccination for infants with HIV only if they are receiving ART.</p> <p>Infants who have contact with a person who has TB – and if they are unlikely to have active TB – should receive TB preventive treatment.</p>
TREATMENT	<p>TB can be cured, regardless of HIV status or CD4 cell count. The type and length of TB treatment depend on whether TB is drug-sensitive or drug-resistant, and the extent of drug resistance.</p> <p>People should start TB treatment before starting (or re-starting) ART.</p> <p>Extrapulmonary TB is treated with the same medicines as pulmonary TB.</p>			



SERIOUS BACTERIAL INFECTIONS

What is it, and what causes it?

Infections happen when harmful bacteria enter a person's body, such as through a cut in the skin, from contaminated food, or inhaled in tiny droplets. Some bacterial infections are sexually transmitted, such as syphilis, chlamydia, and gonorrhea.

People with AHD often have severe bacterial infections, which can happen in the bloodstream, nose, mouth, throat, voice box, windpipe or lungs, the brain and spinal cord or the stomach and intestine.

What are the symptoms?

The symptoms depend on the type of bacteria and where the infection is, but the general symptoms may include:

- » Fever
- » Feeling tired
- » Headache
- » Swollen lymph nodes in the neck, armpit, or groin
- » Nausea
- » Vomiting

Table 2: Summary of care for serious bacterial infections in AHD

	ADULTS (age greater than 19 years) (including during pregnancy)	ADOLESCENTS (age 10-19 years)	CHILDREN (age less than 10 years)	INFANTS (age less than 1 year)
TESTING	Access to testing for serious bacterial infections can be limited; it is sometimes based on signs and symptoms.			
PREVENTION	Daily cotrimoxazole prophylaxis (protection) is recommended for everyone with AHD, whatever age. It protects against some (but not all) serious bacterial infections, malaria, Pneumocystis jirovecii pneumonia and toxoplasmosis. People living where there are high rates of severe bacterial infections and/or malaria should get lifelong cotrimoxazole, whatever their CD4 count.			
	For adolescents and adults with AHD, vaccinations are safer and more effective when CD4 count is greater than 200 cells/ mm3		Pneumococcal conjugate vaccine (PCV) and catch-up vaccinations are recommended for all children living with HIV ages 6 weeks to less than 5 years.	
TREATMENT	Antibiotics can cure bacterial infections. The antibiotic used depends on which bacteria is causing the infection.			



CRYPTOCOCCAL MENINGITIS

What is it, and what causes it?

Cryptococcal meningitis is a serious infection of the brain and spinal cord. It is caused by a tiny fungus in soil that most people inhale every day. A strong immune system can fight off the infection. People with AHD – especially if their CD4 cell count is under 100 cells/mm³ – can become ill with cryptococcal meningitis when this fungus spreads from the lungs to the brain. When it is not treated, cryptococcal meningitis is fatal.

What are the symptoms?

- » Fever
- » Headache
- » Stiff neck
- » Nausea
- » Vomiting
- » Becoming more sensitive to light
- » Confusion
- » Memory loss
- » Personality changes

Table 3: Summary of care for cryptococcal meningitis in AHD

	ADULTS (age greater than 19 years) <i>(including during pregnancy)</i>	ADOLESCENTS (age from 10-19 years)	CHILDREN (age less than 10 years)	INFANTS (age less than 1 year)
TESTING	In people with symptoms, two tests are recommended for diagnosing cryptococcal meningitis. During a lumbar puncture, a hollow needle goes in the lower back to take a sample of the fluid that surrounds the brain and spinal cord (called cerebral spinal fluid, or CSF) and to check its pressure. CrAg testing can be done with blood or CSF.		Testing for cryptococcal meningitis is not advised in children younger than 10.	No recommendations
PREVENTION	Screening for CrAg is recommended for adults and adolescents with a CD4 count under 100 cells/mm ³ and considered if is under 200 cells/mm ³ . Before starting (or re-starting ART), adults and adolescents with a positive CrAg test result should be checked for signs and symptoms of cryptococcal meningitis and treated if necessary. Otherwise, they should receive fluconazole to prevent them from becoming ill with cryptococcal meningitis (called pre-emptive therapy).		Screening and prophylaxis are not recommended since cryptococcal meningitis is uncommon among children.	
TREATMENT	Adults, adolescents and children who have cryptococcal meningitis should be treated with a week of amphotericin B and flucytosine, followed by a week of fluconazole. (Recommended alternatives are: two weeks of flucytosine and fluconazole or two weeks of amphotericin B). People should continue taking fluconazole until they are stable on ART for at least a year, with either an undetectable HIV viral load and CD4 count of at least 100 cells/mm ³ or a CD4 count of at least 200 cells/mm ³ (if viral load testing is unavailable).			



PNEUMOCYSTIS JIROVECI PNEUMONIA (PCP – FORMERLY KNOWN AS PNEUMOCYSTIS CARINII PNEUMONIA*)

What is it, and what causes it?

Pneumocystis jirovecii pneumonia (PCP) is caused by a fungus which is spread from person to person through the air, entering the lungs when people inhale it. Globally, an estimated 95% of people have been infected with PCP. A strong immune system prevents people from falling ill with PCP, but it can be fatal for people with AHD

What are the symptoms?

- » Fever
- » Chills
- » Cough
- » Chest pain
- » Difficulty breathing
- » Tiredness

* The name was changed because *pneumocystis jirovecii* causes PCP in humans (but not other species)

Table 4: Summary of care for pneumocystis jirovecii pneumonia in AHD

	ADULTS (age greater than 19 years) <i>(including during pregnancy)</i>	ADOLESCENTS (age from 10-19 years)	CHILDREN (age less than 10 years)	INFANTS (age less than 1 year)
TESTING	Access to testing is limited, and it can be expensive and invasive. Treatment is often started in people with symptoms of PCP.			
PREVENTION	Daily cotrimoxazole prophylaxis (protection) is recommended for everyone with AHD, regardless of age, to prevent them from falling ill with PCP.			
TREATMENT	PCP can be treated with cotrimoxazole.			



TOXOPLASMOSIS

What is it, and what causes it?

Toxoplasmosis is an infection caused by a parasite found in cat faeces. Toxoplasmosis can be transmitted from mother to infant. It spreads when people eat contaminated raw or undercooked meat and unwashed fruit and vegetables, and from changing a cat litter box.

Globally, up to half of all people have been infected with toxoplasmosis. Toxoplasmosis can affect the brain, eyes, lungs and other organs. A strong immune system prevents people from falling ill. Toxoplasmosis can be fatal for people with AHD, including infants.

What are the symptoms?

- » Headache
- » Confusion
- » Poor coordination
- » Seizures
- » Behavior change
- » Memory loss
- » Weakness
- » Nausea
- » Pain in the eyes
- » Blurry vision or vision loss
- » Sensitivity to light

Table 5: Summary of care for toxoplasmosis in AHD

	ADULTS (age greater than 19 years) <i>(including during pregnancy)</i>	ADOLESCENTS (age from 10-19 years)	CHILDREN (age less than 10 years)	INFANTS (age less than 1 year)
TESTING	Antibody testing is not always reliable, so treatment is usually started based on symptoms and continued if they improve.			
PREVENTION	Daily cotrimoxazole prophylaxis (protection) is recommended for everyone with AHD regardless of age, to prevent them from falling ill with toxoplasmosis.			
TREATMENT	Toxoplasmosis is treated with high dose cotrimoxazole. Other options include pyrimethamine-based treatment (plus sulfadiazine or clindamycin plus folinic acid).			



CYTOMEGALOVIRUS (CMV) RETINITIS

What is it, and what causes it?

Cytomegalovirus (CMV) is a virus. CMV retinitis refers to a CMV infection in the tissue in back of the eyes. CMV can also infect the lungs, liver, stomach, intestines and esophagus (the tube connecting the throat to the stomach).

CMV is spread by direct contact with body fluids (blood, semen, vaginal fluid, breast milk, saliva, urine) from a person with CMV. This contact could be: mother to infant before or during birth, via breastfeeding, or from condomless sex

A strong immune system prevents people from becoming ill with CMV retinitis. People with AHD who have a CD4 count of less than 100 cells/mm³ can develop CMV retinitis, which causes blindness if not promptly diagnosed and treated.

What are the symptoms?

- » Small specks, called floaters, in the eye
- » Flashes of light in the eye
- » Blurred vision
- » Blind spots
- » Loss of peripheral (side) vision
- » Sudden vision loss
- » CMV retinitis usually starts in one eye, but often both eyes are involved.

Table 6: Summary of care for cytomegalovirus in AHD

	ADULTS (age greater than 19 years) <i>(including during pregnancy)</i>	ADOLESCENTS (age from 10-19 years)	CHILDREN (age less than 10 years)	INFANTS (age less than 1 year)
TESTING	Trained healthcare workers can diagnose CMV with an eye exam, but access remains limited.			
PREVENTION	CMV retinitis can be prevented with ART, by keeping CD4 cell count above 100 cells/mm ³ .			
TREATMENT	It can be treated with oral valganciclovir or by injections into the eye.			



Q AND A

QUESTIONS

1. What is advanced HIV disease (AHD)?
2. What are CD4 cells?
3. What are the danger signs for AHD?
4. How can AHD be prevented?
5. Who should get a CD4 test?
6. Who should start ART?
7. What kind of care and treatment should people with AHD have?
8. What test is used for active TB?
9. What test is used for cryptococcal meningitis?
10. What test is used for PCP?
11. What test is used for toxoplasmosis?
12. What test is used for CMV retinitis?

ANSWERS

1. Advanced HIV Disease or AHD means you have or could get certain illnesses that happen when someone has a low CD4 cell count. In adults, adolescents and children over five years old, AHD is a CD4 cell count of less than 200 cells/mm³. All children under age five have AHD.
2. CD4 cells are infection-fighting white blood cells that work with the rest of the immune system.
3. For adults and adolescents, the danger signs include:
 - » Rapid breathing
 - » Rapid heart rate
 - » Not being able to walk without help
 - » High fever (39°C or higher)For children, the danger signs include:
 - » Tiredness
 - » Becoming unconscious
 - » Unable to drink or breastfeed
 - » Repeated vomiting
 - » Convulsions (sudden, violent, irregular movements)
 - » High fever (39°C or higher)
4. Starting ART – or re-starting it – right away gives people with AHD the best chance of getting better and avoiding illnesses, even with a very low CD4 count.
5. Everyone who is diagnosed with HIV or re-entering care should get a CD4 test to check their CD4 count.
6. Everyone should start ART when they are diagnosed with HIV, whatever their CD4 count.
7. People with AHD should receive counselling and adherence support, ART, tests for other infections and medicines to prevent or treat them.
8. Xpert MTB/RIF or a urine test called TB-LAM (for all seriously ill adults, adolescents and children who have AHD or a CD4 cell count of less than 100 cells/mm³ and TB symptoms, including people in the hospital.
9. A lumbar puncture.
10. Since access to testing is limited, treatment is often started without testing in people with symptoms.
11. In people with symptoms, treatment is usually started without testing and continued if people get better.
12. An eye exam by a trained healthcare worker.

How did you do?

- » If you didn't get all the answers the first time, go through the section and test yourself again.
- » How much better did you do?

EXERCISE FOR FACILITATORS



You will need:

1. Post-it notes
2. Marker pens



Divide the participants into six groups.



Give each group a topic (illness):

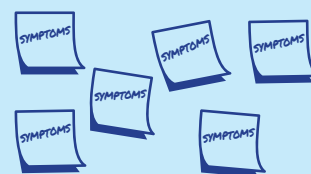
1. TB
2. Serious bacterial infections
3. Cryptococcal meningitis
4. PCP
5. Toxoplasmosis
6. CMV



Ask the participants to write the symptoms of the illness on Post-it notes.



Label one member from each group with the name of the illness.



Mix all the symptoms from the different illnesses up and post on a wall.



Ask all the participants to post symptoms on the back of the participant with the correct illness eg blurred vision on the person being CMV.



When all the notes are posted, check the symptoms are correct for each illness.



How did you do?

FURTHER READING

All references cited as of April 2020

- Clinical Infectious Diseases. Advanced HIV Disease. [Online] Volume 66, Supplement 2. April 2018. Available from https://academic.oup.com/cid/issue/66/suppl_2
- Heiden D, Tun N, Maningding E, et al. Training clinicians treating HIV to diagnose cytomegalovirus retinitis. Bulletin of the World Health Organization [Online] 2014;92:903-908. doi: <http://dx.doi.org/10.2471/BLT.14.142372>
- MSF Access Campaign. Stopping Senseless Deaths. Issue Brief [Online] July 2018. Available from https://msfaccess.org/sites/default/files/2019-02/HIV_Brief_StoppingSenselessDeaths_ENG_2018.pdf
- National Institute for Communicable Diseases. Centre for Vaccines and Immunology. Vaccine Information for Parents and Caregivers. [Online] First Edition November 2016. Available from http://www.kznhealth.gov.za/cdc/NICD_Vaccine_Booklet.pdf
- Oladele R, Otu AA, Richardson MD, Denning DW. Diagnosis and Management of Pneumocystis Pneumonia in Resource-poor Settings. J Health Care Poor Underserved [Online] 2018;29(1):107-158. Available from <https://muse.jhu.edu/article/686957/pdf>
- Panel on Opportunistic Infections in Adults and Adolescents with HIV. Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV. Recommendations from the Centers for Disease Control and Prevention, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America [Online]. January 1, 2020. Available from: https://aidsinfo.nih.gov/contentfiles/lvguidelines/adult_o.pdf
- WHO. Toxoplasmosis Fact Sheet. [Online] 2015. Available from http://www.euro.who.int/__data/assets/pdf_file/0011/294599/Factsheet-Toxoplasmosis-en.pdf?ua=1
- WHO. Consolidated Guidelines on the use of Antiretroviral Drugs for Treating and Preventing HIV. Second Edition. [Online] Geneva 2016. Available from https://apps.who.int/iris/bitstream/handle/10665/208825/9789241549684_eng.pdf?sequence=1
- WHO. Guidelines for Managing Advanced HIV Disease and Rapid Initiation of Antiretroviral Therapy [Online]. Geneva 2017 Available from <https://apps.who.int/iris/bitstream/handle/10665/255884/9789241550062-eng.pdf?sequence=1>
- WHO. Summary of the WHO Position Paper on BCG vaccines: WHO position paper – February 2018 [Online] Geneva 2018. Available from https://www.who.int/immunization/policy/position_papers/PP_BCG_summary_2018.pdf?ua=1
- WHO. Guidelines for the Diagnosis, Prevention and Management of Cryptococcal Disease in HIV-infected Adults, Adolescents and Children [Online] Geneva March 2018. Available from <https://apps.who.int/iris/bitstream/handle/10665/260400/WHO-CDS-HIV-18.2-eng.pdf?sequence=1>
- WHO. Lateral flow urine lipoarabinomannan assay (LF-LAM) for the diagnosis of active tuberculosis in people living with HIV. [Online] Geneva 2019. Available from
- <https://apps.who.int/iris/bitstream/handle/10665/329479/9789241550604-eng.pdf?sequence=1&isAllowed=y&ua=1>
- WHO. Summary of WHO Position Paper on Pneumococcal conjugate vaccines in infants and children under 5 years of age, February 2019 [Online] Available from https://www.who.int/immunization/policy/position_papers/who_pp_pcv_2019_summary.pdf?ua=1
- WHO. WHO consolidated guidelines on tuberculosis: module 1: prevention: tuberculosis preventive treatment. [Online] Geneva March 24 2020. Available from <https://www.who.int/publications-detail/who-consolidated-guidelines-on-tuberculosis-module-1-prevention-tuberculosis-preventive-treatment>