Adult antiretroviral therapy at a glance

Haley Smith, BPharm
Amayeza Info Services

Correspondence to: Haley Smith, e-mail: haley@amayeza-info.co.za

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Abstract
Dealing with the challenges of human immunodeficiency virus (HIV) and acquired immune deficiency syndrome (AIDS) continues to be a major global and regional health priority. According to estimates by the World Health Organization and the Joint United Nations Programme on HIV/AIDS, 35.3-million people were living with HIV at the end of 2012. That same year, 2.3-million people became newly infected, and 1.6 million died of AIDS-related causes. South Africa has the highest number of people living with HIV and AIDS in the world, with approximately 5.4-million affected individuals. It is important to get tested for HIV regularly, and to recognise the symptoms of HIV as soon as possible since early diagnosis and treatment may help to prevent serious illness. Early treatment also reduces the chances of transmitting the virus to others.

Introduction
The human immunodeficiency virus (HIV) infects the cells of the immune system, destroying or impairing their function. Infection with the virus results in progressive deterioration of the immune system, leading to “immune deficiency.” The immune system is considered to be deficient when it can no longer fulfil its role of fighting infection and disease.¹

How do the human immunodeficiency virus and acquired immune deficiency syndrome cause illness?
HIV attacks and destroys a type of white blood cell called a cluster of differentiation 4 (CD4) cell, commonly called the T cell. This cell’s main function is to fight disease. When a person’s CD4 cell count is low, he or she is more susceptible to illnesses as the ability to fight infection is lost.² The advanced stage of HIV infection is called acquired immune deficiency syndrome (AIDS).² People with HIV are said to have AIDS when they develop certain infections or cancers,² or when their CD4 (T cell) count is less than 200 cells/mm³ of blood.²

Who is at risk of acquiring human immunodeficiency virus?
HIV infection is usually acquired through sexual intercourse or exposure to infected blood or bodily fluids. This may occur:¹,²,³
- By sharing needles or syringes that have been used by an infected person
- By transmission from a pregnant woman to her baby during pregnancy, birth or breastfeeding, although this is uncommon if HIV medication is taken during and after pregnancy.

HIV infection is not spread by casual contact.³ A person cannot acquire HIV from sharing cups, utensils, telephones, bathrooms or swimming pools with someone who has HIV or AIDS.²

Symptoms
It is important to recognise the symptoms of HIV as soon as possible, since early diagnosis and treatment may help to prevent serious illness. Early treatment also reduces the chances of transmitting HIV to another person.³,⁵ The length of time for an infected person with HIV to develop AIDS varies widely in individuals. Left untreated, the majority of people who are infected with HIV develop signs of HIV-related illness within 5-10 years, although this can be shorter. The time between acquiring HIV and an AIDS diagnosis is usually between 10 and 15 years, but may be longer.¹

The symptoms of HIV and AIDS vary, depending on the phase of infection.⁶

Symptoms of early human immunodeficiency virus infection
Early symptoms of HIV infection develop in 50-90% of people who are infected, usually beginning 2-4 weeks after exposure to HIV.
The initial group of signs and symptoms are referred to as primary or acute HIV infection.

Because the signs and symptoms of primary HIV may be mild enough to go unnoticed or are similar to those of other common illnesses, such as the flu, initially most people do not realise that they are infected with HIV. However, HIV infection is highly contagious at this early stage because the amount of virus in the bloodstream (viral load) and other bodily fluids is particularly high at this time. As a result, HIV infection spreads more efficiently during primary infection than during the next stage of infection.

**Body-wide symptoms**

The most common body-wide signs and symptoms of primary HIV include the following:

- Fever
- Headaches
- A sore throat
- Muscle and joint pain.

These flu-like symptoms last approximately two weeks. During the second week of the illness, most people also experience painless swelling of certain lymph nodes, including those in the armpits and neck. Although the lymph nodes decrease in size after the first few weeks, swelling may linger.

**Digestive symptoms**

Many people with primary HIV infection develop diarrhoea, nausea and vomiting, lack of appetite and weight loss.

**Skin, mouth and genital symptoms**

A characteristic feature of primary HIV infection is painful open ulcers or sores which may develop in the mouth, or on the oesophagus, penis or anus. Many people also develop a rash which usually affects the face, neck and upper chest. However, the skin rash may be more widespread. The skin rash usually appears 2-3 days after the fever and lasts approximately 5-8 days.

**Respiratory symptoms**

A dry cough may be associated with primary HIV infection.

**Symptoms of advanced human immunodeficiency virus infection**

If HIV is not treated, the virus causes progressive weakening of the immune system. It may take several years for significant damage to occur. This makes the person more susceptible to opportunistic infections. These opportunistic infections can cause serious disease in patients with advanced HIV infection.

One of the most common opportunistic infections is yeast infection of the mouth or oesophagus which is caused by *Candida*, a fungal organism that is normally found on the skin and in the mouth, intestinal tract and vagina in healthy individuals. *Candidiasis* of the mouth, also known as thrush, causes cream-coloured, slightly raised patches in the mouth, soreness and easy bleeding. *Candidiasis* of the oesophagus may cause difficulties with swallowing. Depending on the opportunistic infection, other symptoms can include blurred vision, fever, weight loss or shortness of breath.

**An overview of the management and treatment of human immunodeficiency virus**

HIV is a type of virus known as a retrovirus. Retroviruses contain several targets that are disrupted by medicines that treat HIV. Medications used to treat HIV are called antiretroviral therapy (ART). ART can slow the disease progression by preventing the virus from replicating and therefore decreasing the amount of virus in an infected person's blood.

The time to start ART for HIV depends upon several factors, including the T-cell count, underlying medical condition, age, the history of an AIDS-defining illness and the willingness of the patient to commit to lifelong treatment. To a large extent, the urgency in starting treatment is based on the T-cell count. The lower the T-cell count, the more urgent it is that treatment is started. Treatment of HIV also prevents its transmission.

Therefore, successful treatment nearly eliminates the risk of transmission to an unborn child during pregnancy or sexual transmission to an uninfected partner.

The goal of treating established HIV infection with ART is to achieve durable suppression of replication, i.e. an undetectable viral load, to allow immune recovery and to reduce morbidity and mortality and increase quality of life.

Table I lists some guidelines for commencing ART.

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<th><strong>Table I: Guidelines for commencing antiretroviral therapy</strong></th>
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<tr>
<td>Eligibility criteria</td>
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<td>- CD4 count &lt; 350 cells/mm³, regardless of stage or symptoms</td>
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<tr>
<td>- World Health Organization stage 3 or 4 or other serious morbidity, regardless of CD4 count</td>
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<tr>
<td>- Multidrug-resistant or extensively drug-resistant tuberculosis, regardless of CD4 count</td>
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Note: The National Department of Health guidelines are more conservative owing to resource constraints.

**A review of antiretroviral therapy**

There are several classes of ART.

**Nonnucleoside reverse transcriptase inhibitors**

Nonnucleoside reverse transcriptase inhibitors (NNRTIs) directly inhibit the activity of the enzyme, reverse transcriptase. They potently suppress HIV by disabling the protein needed to replicate itself. High-level resistance develops rapidly, and they must always be used in combination, usually with two nucleoside or nucleotide reverse transcriptase inhibitors (NRTIs). Cross-resistance within the class may occur. Examples include nevirapine, efavirenz and etravirine.
**Nucleoside or nucleotide reverse transcriptase inhibitors**

NRTIs are nucleoside analogues which are incorporated into the DNA of HIV. They act as false substrates for reverse transcriptase and terminate the DNA chain. In other words, NRTIs are faulty versions of building blocks that HIV needs to make copies of itself. Examples include abacavir, didanosine, lamivudine, stavudine, zidovudine and emtricitabine. The NRTI inhibitor, tenofovir, acts in the same manner.

The combination of stavudine and zidovudine, which are both thymidine analogues, is antagonistic, and should be avoided.

If possible, two NRTIs with similar adverse effects should not be combined, e.g. didanosine and stavudine, as both are associated with a higher risk of hyperlactataemia.

Tenofovir increases the concentration of didanosine, but even with a dose reduction this combination is less effective than other dual NRTI combinations and is best avoided.

Emtricitabine and lamivudine share the same resistance pathway and should not be used together.

**Protease inhibitors**

Protease inhibitors (PIs) inhibit the HIV protease enzyme which prevents cleavage of viral polyproteins and results in immature, non-infectious HIV viral particles, thus suppressing HIV replication. Examples include atazanavir, darunavir, fosamprenavir, indinavir, lopinavir, neflinavir, ritonavir and saquinavir. There is cross-resistance between some of these drugs. They undergo hepatic cytochrome P450 metabolism, and most, especially ritonavir, are potent hepatic enzyme inhibitors.

Garlic supplements, milk thistle and St John’s wort substantially reduce the concentrations of certain PIs. PIs may also cause metabolic abnormalities, such as hypercholesterolaemia, hypertriglyceridaemia and insulin resistance. Atazanavir and saquinavir have a low risk of dyslipidaemia.

PIs must always be used in combination, and are usually reserved for second-line therapy if the initial treatment regimen of two NRTIs and one NNRTI fails.

**Integrase strand transfer inhibitors**

Raltegravir is an HIV integrase strand transfer inhibitor (INSTI). It works by disabling the integrase protein. This prevents the insertion of viral DNA into CD4 cells. Raltegravir was the first available drug in this class, and is effective in patients who are starting their first HIV regimen, as well as in patients who have been treated in the past. Raltegravir is a third-line regimen in the South African ART guidelines.

**Fusion inhibitors**

Entry or fusion inhibitors are not usually included in initial treatment. These drugs block the entry of HIV into CD4 cells.

Examples include enfuvirtide and maraviroc.

ART regimens are commonly referred to as having a backbone and a base. As an example:

- The backbone typically consists of two NRTIs.
- The base is either a NNRTI, or an INSTI.

Patients usually start with a combination of three HIV medications, which usually includes an NNRTI, plus two NRTIs. Sometimes two or three of these medicines are combined in one tablet. Each class of medication has a specific task which works best when it is combined with another class of medication. The decision about which medications to use will depend on many issues, such as whether or not there is drug resistance to any HIV medication.

Tenofovir plus lamivudine, or emtricitabine plus nevirapine or efavirenz, is currently the nationally recommended first-line regimen. Second-line therapy usually involves replacing nevirapine or efavirenz with a PI combination, e.g. lopinavir and ritonavir, and replacing the NRTIs.

**Side-effects of antiretroviral therapy**

Side-effects from ART are relatively common. However, most resolve within the first three months of therapy. Lipodystrophy, a fat maldistribution, is a common late complication with ART. The loss of fat has been linked to the thymidine analogue NRTIs, stavudine and zidovudine.

**Conclusion**

Although HIV and AIDS cannot be cured, the treatment of HIV infection has been revolutionised by potent ART. Use of multidrug regimens has resulted in a substantial reduction in progression to AIDS, opportunistic infection, hospitalisation and death.

**References**