

The management of HIV: A practical approach

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Highlights

- How is HIV diagnosed?
- What are the stages of HIV?
- What special investigations need to be done?
- What is important in the physical examination?

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Introduction

This is the first article in a series on the clinical management of patients infected with the Human Immunodeficiency Virus (HIV). This paper focuses on the diagnosis, staging and physical examination of the patient, while the following two articles will address the prophylaxis and treatment of opportunistic infections. Thereafter an article will deal with antiretrovirals and finally ethical issues regarding HIV will be discussed.

Ultimately the profound immune suppression resulting from HIV infection renders patients vulnerable to opportunistic infections and malignancies. The median time from infection to Acquired Immunodeficiency Syndrome (AIDS) is 8-10 years in developed countries, but there is individual variation with a small proportion of patients progressing very fast, and a smaller proportion of patients who remain clinically stable, the so-called non-progressors.¹ Poor socio-economic circumstances and malnutrition can shorten the time duration from primary HIV infection to AIDS.

The CD4 count plays an important role in gauging damage to the immune system and cannot be left unmentioned in a discussion on the clinical staging of HIV, although it

will be discussed at length later in the article.

STAGING OF HIV

The immunodeficiency that develops during HIV infection is a continuum, but several discrete clinical phases can be identified. Understanding the natural history of HIV infection allows the doctor to make treatment decisions based on the clinical presentation of the patient.

The World Health Organization (WHO) uses standardised criteria to clinically stage HIV infection, as seen in **Table I**. This staging accommodates facilities where CD4 testing is not freely available and thus only uses patient clinical determinates.

WHO Stage 1

The acute retroviral syndrome is usually symptomatic. Patients mostly present with symptoms resembling 'flu or infectious mononucleosis. The symptoms are usually dismissed as a common cold or 'flu by the patient and physician; thus very few patients are diagnosed during seroconversion. Infrequently the patient may present with an opportunistic infection at this stage.

The so-called asymptomatic HIV stage may last for a number of years. Most of these patients are

Table I: The World Health Organization Clinical Staging System for HIV.

WHO Stage 1

- Acute retroviral infection
- Asymptomatic infection
- Persistent generalised lymphadenopathy
- *Performance scale 1:* asymptomatic with normal activity

WHO Stage 2

- Weight loss < 10% of body weight
- Minor mucocutaneous manifestations
- Herpes zoster shingles
- Recurrent upper airways infections
- *Performance scale 2:* symptomatic with normal activity

WHO Stage 3

- Weight loss > 10% of body weight
- Unexplained chronic diarrhoea > 1 month
- Unexplained prolonged fever (intermittent or constant) > 1 month
- Oral candidiasis
- Vulvovaginal candidiasis
- Oral hairy leukoplakia
- Pulmonary tuberculosis
- Severe bacterial infections
- *Performance scale 3:* in bed <50% of normal daytime during past month

WHO Stage 4, AIDS-defining conditions

Cancers

- Lymphoma
- Kaposi's sarcoma (KS)
- Invasive cervical cancer

Bacteria

- Extrapulmonary tuberculosis
- Atypical mycobacteriosis
- Pneumocystis jiroveci pneumonia (PCP)
- Recurrent pneumonia
- Salmonella septicaemia
- Toxoplasmosis

Fungal infections

- Candidiasis of the oesophagus, trachea, bronchi or lungs
- Cryptosporidiosis
- Intestinal isosporiasis or mycosporidiosis
- Cryptococcus meningitis
- Other systemic mycosis

Viral infections

- Cytomegalovirus (CMV)
- Herpes simplex virus ulceration > 1 month
- HIV encephalopathy

Other

- Progressive multifocal leuko-encephalopathy
- HIV wasting syndrome
- *Performance scale 4:* In bed > 50% of daytime during the past month

unaware of their status, and if sexually active, proceed to infect others.

Persistent generalised lymphadenopathy (PGL) is the presence of lymphadenopathy in two sites other than inguinal for a period longer than six months.

WHO Stage 2

A number of clinical manifestations of autoimmune responses to HIV can be found in the patient even in early disease. These include arthritis, anaemia, glomerulonephritis, thrombocytopenia, neuropathies and disturbances of coagulation. This is due to the chronic and acute activation of the immune system by the HIV where immunoglobulins are not effectively cleared from the body.

At this stage patients may also develop a range of minor dermatological conditions of which some are immune related, for example prurigo, acne and seborrhoeic dermatitis. Other skin conditions include fungal nail infections and recurrent oral ulceration. At this stage the patient may experience the first attack of herpes zoster shingles (**Figure 1**).



Figure 1: Untreated herpes zoster of the 5th cranial nerve.

This is a flare up of a previous herpes zoster infection (chicken pox as a child) and not a reinfection with the virus. Upper respiratory tract infections are common, especially sinusitis. Patients are also at an increased risk of idiosyncratic drug reactions.

WHO Stage 3

Anorexia, significant weight loss, night sweats and malaise may occur as the disease progresses, even in the absence of opportunistic disease.

Chronic diarrhoea is a feature of

this stage and should be investigated for other possible infective organisms before ascribing it to HIV. Systemic bacterial infections such as pneumonia and pyelonephritis are also more frequent.

Recurrent oral candidiasis and oral hairy leukoplakia can occur. Vulvovaginal candidiasis may be chronic or poorly responsive to topical therapy.

Pulmonary tuberculosis (PTB) can appear in patients at any CD4 count. The presentation is more typical (**Figure 2**) in patients with higher CD4 counts, while in patients with very low CD4 counts it can be extremely difficult to confirm a diagnosis of PTB because of the atypical presentation of the disease.

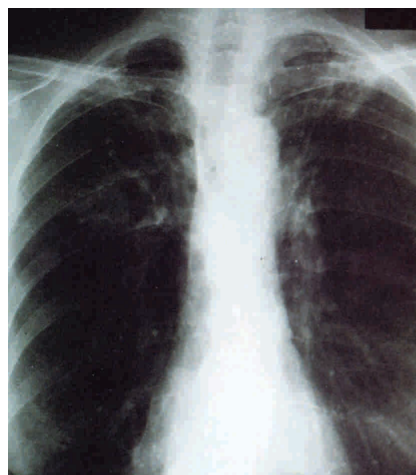


Figure 2: Pulmonary tuberculosis with fibrosis.

WHO Stage 4

This stage includes all the Acquired Immune Deficiency Syndrome (AIDS) defining conditions. AIDS is diagnosed should any *one* of these conditions be present.



Figure 3: Discrete Kaposi's lesion on the hand.



Figure 4: Disseminated Kaposi's sarcoma.

Kaposi's sarcoma (**Figures 3 and 4**) is associated with Human Herpes virus type 8. It is regarded as AIDS defining, even if the CD4 count is above 200 cells/L. It may present as discrete purple to brown-black patches on the skin, but can infiltrate any mucocutaneous surface, including the gastrointestinal tract and lungs. Infiltration of lymph glands cause lymphoedema.



Figure 5: Molluscum contagiosum.

Molluscum contagiosum, (**Figure 5**) although not included in the WHO stage 4 conditions, is a sign of advanced disease and is more extensive the more advanced the immune suppression is. It is caused by a pox virus and presents as dome shaped papules with central dimpling.

Pap smears in female patients are very important since cervical intra-epithelial neoplasia (CIN) lesions quickly progress to invasive cervical cancer.

The WHO regards extrapulmonary tuberculosis as AIDS-defining. Extrapulmonary presentations of TB include TB pleuritis, TB lymphadenitis (**Figure 6**), TB meningitis and miliary TB. *Mycobacterium avium* disease, *Toxoplasma gondii*, Cryptosporidium and Cytomegalovirus



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Figure 6: Tuberculous lymphadenitis.



Figure 7: Herpes simplex ulceration of the lip.

infections usually present at CD4 counts below 50 cells/L. Some of the atypical fungi that may occur include histoplasmosis, coccidioidomycosis, aspergillosis and mucormycosis.

Herpes simplex ulceration (*Figure 7*) is frequently seen in earlier stages of HIV, but in stage 4 it presents as chronic ulceration.

In patients with low CD4 counts a clinician would have a high index of suspicion and actively investigate for opportunistic infections should the patient be symptomatic.

DIAGNOSING HIV INFECTION

Offering HIV testing to a patient

As HIV has a high seroprevalence in South Africa, most physicians are aware of signs and symptoms of advanced HIV disease and would offer such a patient an HIV test. However, many individuals may not display overt clinical signs and symptoms of HIV infection and the physician should have a high index

of suspicion. The question arises: when should a physician offer HIV testing to a patient?

Clinical indications for HIV testing:

- Any probable viral illness warrants questions about risk factors and recent sexual exposure.
- Any two people embarking on a new relationship
- All pregnant women and any couple planning a family.
- Any patient presenting with a possible opportunistic infection such as herpes zoster shingles or tuberculosis.
- Any patient presenting with an STI syndrome

Consider HIV testing when certain abnormal blood results are found:

- A finding of an increased total serum protein with a normal to decreased serum albumin on routine testing of liver functions, reflecting hypergammaglobulinaemia. (Hypergammaglobulinaemia in HIV is due to uncontrolled B-cell replication.)
- Normocytic to mildly microcytic anaemia.

Pre and post-test counselling and informed consent must always accompany HIV testing.

Establishing the diagnosis

Anti-HIV antibody tests are currently recommended for routine diagnosis of HIV infection in South Africa.² Two to three different enzyme-linked immunosorbent assay (ELISA) tests are used for confirmation.³ A second specimen should be tested to rule out any mistake on the part of the physician or the laboratory. The third generation ELISA tests being used currently have a sensitivity approaching 100% and a specificity of more than 99%. On rare occasions, false positive and false negative results may occur. Should a clinician be uncertain of the interpretation of the result of the anti-HIV antibody test, she/he must consult

a virologist. The window period, that is the time from infection until antibodies become detectable in the blood with diagnostic tests, is currently three to four weeks for the third generation ELISA tests.

The Western blot assay is still used by many laboratories as a confirmatory test, but is labour intensive and sometimes gives indeterminate results.^{2,3}

On site testing can be done using two different types of rapid tests, according to the World Health Organization. The blood is obtained through a finger prick. The accuracy is close to that of the ELISA tests, if performed exactly according to instructions. Further laboratory testing must be performed for doubtful results. On site testing has certain advantages, including a quick turn around times for results. It also caters for the group of patients who would not have returned for their results.

Whereas all the previous tests test for anti-HIV antibodies, the HIV DNA polymerase chain reaction (PCR) test is a qualitative molecular assay that determines whether the HIV is present in peripheral blood mononuclear cells. It is thus reported as positive or negative.

The test is used for the following indications:

- to determine viral infection in infants under the age of 18 months born to HIV-positive mothers (HIV ELISA might be falsely positive since the mother's HIV antibodies cross the placenta during pregnancy), and
- early determination of infection in sexual assault or rape cases.

PCR testing can detect HIV in the blood approximately two weeks after infection.

Laboratory monitoring of HIV disease

Laboratory tests can be used to determine disease progression as

well as response to antiretroviral therapy. The most useful tests include the viral load and the CD4 count.⁴ Ideally both the viral load and CD4 count should be requested; however in resource constrained situations the CD4 count is the most useful and viral load testing can be delayed until initiation of antiretrovirals. These tests are done as baseline investigations and thereafter at yearly to six-monthly intervals. These tests should not be done during an acute illness or within a few weeks of a vaccination.

The CD4 count

T-lymphocytes are divided into CD4 and CD8 cells, depending on the receptor present on the cell surface.

The CD4 positive T-cells organise and amplify the immune response, while the CD8 positive T-cells destroy foreign organisms. CD4 is also a major receptor for HIV, thus cells with a CD4 receptor, such as the CD4 positive T-lymphocytes, are infected and directly destroyed by HIV.

The CD4 count is used as a reflection of the damage incurred by the immune system as well as immune system restoration in patients on antiretroviral therapy.

The CD4 count is expressed as an absolute number or a percentage of T-lymphocytes. The absolute CD4 count is subject to considerable variation and therefore a trend in a series of CD4 counts has more application than any one result. The CD4% is less subject to variation on repeated measures.

Table II reflects the relationship between CD4 count, CD4% and immune suppression in adults. The normal CD4 count in children is age dependent and CD4% should rather be used. In some instances where

CD4 counts are unobtainable, the absolute lymphocyte count may give a rough guide to what the CD4 count may be. An absolute lymphocyte count of $1.25 \times 10^9/L$ correlates roughly with a CD4 count of less than 200 cells/L.

The CD4 count declines at an average of 40-80 cells/L per year. A more rapid drop of CD4 cells is associated with faster progression to AIDS.

The viral load

The quantitative HIV-1 RNA PCR assay (viral load) measures plasma free HIV-1 virus. Three main types of viral load tests are used by the majority of laboratories that differ slightly in results; it is therefore advisable to use one laboratory and one test type for follow-up monitoring of a patient. Viral load measurements have made it possible to predict time to progression to AIDS as well as to determine how effective antiretroviral drugs are in lowering the viral load.

The viral load is a quantitative measure that can be expressed in two ways:⁵

- the number of HIV-1 RNA copies/ml of plasma, or
- the logarithmic equivalent – \log_{10} equivalent.

Only a change of more than $0.5\log_{10}$ is regarded as clinically significant.

As an example: a change in viral load from 10 000 to 100 000 copies/ml represents a $1 \log_{10}$ change and is regarded as clinically significant, whereas a change in viral load from 10 000 to 30 000 copies/ml represents a $0.48 \log_{10}$ change and is not clinically significant.

Table II: The CD4 count, CD4% and immune suppression in adults.

| CD4 positive cell count/L | CD4 percentage | The immune system |
|---------------------------|----------------|-----------------------------|
| >500 | >29 | Normal immune function |
| 200-499 | 14-28 | Moderate immune suppression |
| <200 | <14 | Advanced immune suppression |
| <50 | | Severe immune suppression |

THE INITIAL CLINICAL EVALUATION OF THE PATIENT

The initial evaluation should include:

- A complete history and physical examination.
- Full blood count.
- Serum transaminases.
- CD4 count.
- HIV viral load.
- Syphilis serology.
- Pap smear for female patients.

Mild cytopenia and mildly raised liver transaminases are frequently seen.

Considering the financial implications of an HIV viral load test, it can be delayed until initiation of antiretrovirals.

FREQUENTLY SEEN PHYSICAL SIGNS

Symptoms and signs are dependent on the stage of presentation. Patients with acute seroconversion will have different presenting symptoms and signs in comparison to patients with advanced HIV. These are non-specific generalised symptoms and signs that need interpretation in the light of a high index of suspicion. It is of particular importance to note that symptomatic disease can occur at any stage of HIV disease irrespective of CD4 cell counts.

Table III summarises physical signs and symptoms associated with HIV disease.

A complete physical examination should always be done at follow-up, but special attention should be

Table III: Signs and symptoms associated with HIV disease.

| Stage | Symptoms | Signs |
|--------------------------|---|---|
| Seroconversion | Fever, malaise, lethargy, anorexia, weight loss, arthralgias, myalgias, nausea, vomiting, diarrhoea headache. | Fever, pharyngitis, lymphadenopathy, meningitis, encephalitis, myelopathy, erythematous maculopapular rash, mucocutaneous ulceration. |
| Symptomatic stage | Dermatological | |
| | Pruritis, rash, eruption, pain. | Seborrhoeic dermatitis, folliculitis, shingles, Molluscum contagiosum, ulcers – mucosal and gluteal cleft, straightening/softening/loss of hair, Kaposi's sarcoma. Pruritic papular eruption of HIV |
| | Oropharynx | |
| | Generally asymptomatic, ulcers may be painful. | Thrush, hairy leukoplakia, aphthous ulcers, Kaposi's sarcoma. |
| | Respiratory | |
| | Cough (may be non-productive), dyspnoea, fatigue, weight loss, night sweats. | Acute bronchitis, sinusitis, pneumonia, pleural effusions. Neoplastic – Kaposi's sarcoma and lymphoma, diffuse parenchymal lung disease |
| | Cardiovascular | |
| | Dyspnoea, orthopnoea, palpitations | Heart failure: dilated cardiomyopathy, pericardial effusions, aneurisms, vasculitis |
| | Gastrointestinal | |
| | Nausea, vomiting, increased bowel movements, odynia/dysphagia. | Oesophageal ulcers, Kaposi's sarcoma, lymphoma, gastroenteritis, colitis. |
| | Hepatobiliary | |
| | Jaundice, pain in left hypochondrium. | Hepatosplenomegaly, jaundice, pancreatitis. |
| | Kidney/genitourinary tract | |
| | Dysuria, genital pruritis, discharge, occasionally oedema. | Renal failure, proteinuria, oedema (rare), nephritic syndrome, genitourinary tract infections, vulvovaginal candidiasis. |
| | Rheumatological | |
| | Painful joints, dry eyes and mouth, myalgias. | Arthralgia, reactive arthritis, Sjögrens syndrome, fibromyalgia. |
| | Haematopoietic system | |
| | Progressive fatigue and dyspnoea. | Anaemia, thrombocytopenia (petechia and bleeding), features of neutropenia. |
| | Neurological | |
| | Painful limbs (mostly legs), decreased mentation, confusion, headache. | Peripheral neuropathy, meningitis, encephalitis, stroke syndromes, myelopathies, myopathy. |
| | Ophthalmologic | |
| | Painless visual loss, floaters, may be painful when associated with herpes | Cotton wool spots, haemorrhage, retinitis. |

paid to the mouth, lymph nodes and the feet, as well as any signs that may point to systemic opportunistic infections.

The mouth

HIV infection is associated with a

variety of oral lesions⁶ and oral manifestations are often the first clinical expression of HIV infection in an individual.⁷ Examination of the oral cavity can give some indication of the status of the immune system. The history should always

include questions on appetite, taste and any oral pain or dysphagia.

Table IV summarises oral manifestations of HIV disease.

Table IV: Common oral manifestations of HIV disease.

| Fungal | Candidiasis |
|------------|--|
| Viral | Herpes simplex Herpes zoster Hairy leukoplakia |
| Bacterial | Gingivitis |
| Malignancy | Kaposi's sarcoma |
| Other | Aphthous ulcers |

Lymphadenopathy

Intense immune activity early in the HIV infection leads to lymph node hyperplasia and lymphadenopathy.

As the disease progresses, the lymph node architecture is destroyed causing lymphadenopathy to disappear in later stages of disease. In some patients the lymphadenopathy reappears on initiation of antiretrovirals, since prior to AIDS, the immune system has a degree of self-regeneration.

Indications for further investigation (preferably lymph node excision) into lymphadenopathy include:

- Lymph nodes > 2 cm in greatest diameter.
- Painful lymph nodes.
- Lymphadenopathy accompanied by anaemia/ high ESR.
- New onset of clinical disease.

Lymph node aspiration can be done in the practitioner's rooms, but in the author's experience, a lymph node excision is often necessary to come to a diagnosis.

The differential diagnosis of such lymph nodes would include:

- Progressive generalised lymphadenopathy.
- Tuberculous lymphadenitis.
- Lymphoma.
- Fungal infection.
- Metastatic carcinoma.

Change in body weight

A patient should be weighed at every visit to the clinic and a loss of weight should trigger more intensive review of the history and a more focused physical examination for possible causes of loss of weight. Stable patients can also gain weight, as could patients starting on antiretrovirals.

Peripheral neuropathy

Peripheral neuropathy can be very debilitating for a patient. Mostly it presents as a sensory peripheral neuropathy. The patient may volunteer numbness or a burning sensation at the bottom of the feet or a feeling of pins and needles. In more advanced cases the patient may have difficulty in walking. HIV is one of the diseases that cause peripheral neuropathy, but a number of drugs, including tuberculostatics and some antiretrovirals may also be the cause.

The clinical picture and treatment of opportunistic infections will be dealt with in the next two issues.

COUNSELLING IN THE CONTEXT OF HIV

The diagnosis of HIV is devastating for a patient. We are not dealing with a disease, but with a patient with a disease. The patient has a family and friends, a home and

(hopefully) a job.

HIV counselling not only conveys knowledge about the disease, but also provides a supportive environment for the patient. The patient needs help in dealing with problems and issues. The physician cannot provide quick answers, but must help the patient to develop coping skills. Counselling is an ongoing process and does not end after the diagnosis is given. The patient may need counselling in all stages of the disease. The family may also need bereavement counselling. An excellent article to consult on this subject, is by LG Bekker.⁸

See CPD Questionnaire, Page 45

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