updAIDS in SA Family Practice

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*upd*AIDS in SAFP

Based on UNAIDS statistics, there are about 45 million HIV infected people around the world. A national, community based survey suggests that in South Africa the HIV prevalence in the general population is approximately 12% - 12.8% in females and 9.5% in males.[1] Even more alarming are the results of a study which demonstrated that 15.7% of healthcare workers employed in public and private health facilities in four South African Provinces are infected with HIV.[2] With modern antiretroviral (ARV) treatment regimens, sustained high survival rates can be expected.[3,4] Effective management entails lifelong adherence and commitment by patient and service provider to complex treatment, with significant side-effects.

HIV medicine is evolving more rapidly than any other field of medicine. There is thus a need for healthcare professionals to have regular and reliable access to guidelines, new information, updates and continuing medical education. An ever-growing number of organisations offer courses on the management of HIV and there is a plethora of information available. This new SAFP *updAIDS* column will appear bi-monthly and address relevant issues that are of particular importance to family physicians, general practitioners and all other primary care givers. It will provide up-to-date information and guidelines for practice in primary care settings, including the most remote rural areas in Southern Africa and other developing countries. It will attempt to cover the following important topics:

- When should I suspect HIV and how do I diagnose it?
- What can I do for my patient who is infected with HIV?
- What can I do to promote immune function and delay the need for antiretroviral therapy (ART)?
- When should I initiate ART and how should I proceed after starting?
- What should I do if ART is not available?
- What do I do about common HIV-associated mucocutaneous conditions?
- How can I prevent opportunistic infections?
- How should I treat HIV-associated opportunistic infections?

As this column develops you may suggest additional relevant topics that are of concern to you. Some of these issues may be addressed in a letters section, whereas others may be covered in a full article. I hope you will take this opportunity to contribute to the success of this venture.

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Views on news: TAC vs. Rath

At the time of writing this column the most talked about issue was the court case between Matthias Rath and the treatment action campaign (TAC). The TAC and Rath were involved in a legal battle over the controversial dissident's widely publicised claims that the TAC is a front for the pharmaceutical industry.

Rath's company, which sells vitamin products, recently paid for advertisements in the US and South Africa that suggest that antiretroviral therapy is toxic and that the drugs "severely damage all the cells in the body – including white blood cells – thereby worsening immune deficiencies and expanding the AIDS epidemic". The advertisements say the claims are backed by findings from a Tanzanian study by the Harvard School of Public Health. Scientists from the Harvard School of Public Health in the US have condemned businessman Matthias Rath for "deliberately misinterpreting" their research on the benefits that vitamin therapy can offer people infected with HIV. "We condemn these irresponsible and misleading statements," said study authors Wafaie Fawzi and Professor David Hunter in a statement issued in Boston. "It is important to underscore that multivitamin supplements should not be considered an alternative to antiretroviral therapy, but as a complementary intervention that is part of a comprehensive care package," the scientists said.

The heat is on for the controversial Rath Foundation. First, former Education Minister Kader Asmal lambasted "AIDS denialist" Dr Matthias Rath, saying, "His kind of quackery deserves the old Afrikaans response: voetsek." Asmal stepped into the row over Rath's public attacks on the TAC and defended the TAC's "good faith" in the fight against HIV/AIDS. In stark contrast to Health Minister Manto Tshabalala-Msimang's support for the discredited vitamin seller, Asmal has emphatically said he does not want anything to do with Rath or his organisation. Secondly, they have to defend a High Court defamation suit against the TAC and thirdly, the Medicines Control Council (MCC) has announced that it is investigating the foundation's activities in South Africa.

MCC registrar Humphrey Zokufa said the investigation by the Council and the Department of Health was in response to a complaint from the TAC. Zokufa said there "was a sense of urgency" to complete the investigation. The TAC's Zackie Achmat said, "They (MCC) have been aware of the Rath Foundation's activities for at least six months. Their delays have undermined science, the government's antiretroviral programme and allowed Rath to unlawfully experiment on African people to sell his vitamins."

Diagnosing HIV infection

As HIV has a high seroprevalence in Sub-Saharan Africa, most primary care providers will recognise a patient with advanced disease quite readily and offer voluntary counselling and testing (VCT) to confirm the suspected diagnosis of HIV infection. Modern antiretroviral therapy (ART) results in decreased opportunistic infections, increased disease free time survival and decreased mortality.[1,2] However, patients with early disease do not present with the same features seen in advanced disease. It is also, however, of the utmost importance to also diagnose HIV infection in these individuals. Firstly, the infected person can take steps so as not to infect others, and secondly, steps may be taken to preserve the immune status for as long as possible so as to delay the initiation of ART. The diagnosis of HIV infection begins with the recognition and identification of people at risk of infection (see Table 1). Many people with HIV infection are asymptomatic when they first visit a clinician. In such cases it is particularly important for the clinician to be proactive in obtaining the information required to make a valid assessment of the risk of HIV infection. This assessment should be based on knowledge of the local community as well as individual living circumstances, lifestyle information where it is pertinent, and clinical observations. For patients who do not display overt symptoms or signs of HIV infection, the physician needs to have a high index of suspicion and, in addition, needs to take a careful history and obtain information pertinent to the present and past medical history, including family history, and the social and vocational circumstances of the patient.

Table 1: Key factors leading to suspicion of HIV infection

High risk exposures • High prevalence in source population • Unsafe and/or promiscuous sex • Sex with commercial sex workers or other individuals at high risk of HIV • Intravenous drug use • Blood or blood product transfusion (occurring before these were screened for HIV)
Clinical features suggestive of acute HIV disease • Monospot (Paul-Bunnell) negative mononucleosis syndromes • Viral syndromes with truncal maculopapular rash • Aseptic meningitis • Bell's palsy
Constitutional symptoms suggestive of HIV disease • Weight loss (> 4kg over period of 3 months or > 10% of body weight) • Fatigue • Malaise • Fever and /or night sweats
Generalised lymphadenopathy
Dermatological manifestations • *Varicella zoster* • *Seborrhoea* • *Dry skin* • *Folliculitis* • *Psoriasis* • *Molluscum contagiosum* • *Pruritic eruptions* • *Superficial dermatophytosis* • *Warts*
Mucocutanous involvement • Oral or prolonged genital candidiasis • Severe or frequently recurrent oro-labial or genital herpes simplex • Aphthous stomatitis • Oral hairy leukoplakia • Necrotising gingivitis • Condylomata acuminata • Cervical intraepithelial neoplasia

The majority of people in Africa with HIV infection present with symptoms when they first visit a clinician. Among these, some will be exhibiting signs and symptoms of acute infection, but most will have advanced immunodeficiency. In such cases it is particularly important for the clinician to realise that the patient does not necessarily know the cause of his or her symptoms. Even when lifestyle information, reported symptoms, clinical observations and knowledge of the local community all strongly suggest a diagnosis of HIV infection, other potential diagnoses should not be disregarded, especially if these are more easily treated or likely to cause less distress to the patient.

The all-so-important question that needs to be considered is who should be offered VCT and when should a patient be tested for HIV (see Table 2).

Table 2: Indications for voluntary counselling and testing (VCT)

• Patients presenting with high risk lifestyle or physical condition suggestive of HIV • Patients exposed to a sexual assault • Any two people embarking on a new relationship • Couples planning a family • Pregnant women • Patients presenting with any sexually transmitted infection (STI) • Patients presenting with pulmonary or extrapulmonary TB • Patients with chronic diarrhoea lasting for more than 3 weeks • Patients with recurrent upper respiratory tract infections or serious bacterial infections such as pneumonia or meningitis • Patients presenting with other opportunistic infections or AIDS related neoplasms • Patients with abnormal blood results such as: a. High total protein due to hypergammaglobulinaemia (high globulin with normal or low albumin) b. Thrombocytopenia c. Leukopenia, lymphopenia and/or neutropenia d. Normocytic normochromic or mildly microcytic anaemia
Pre- and post-test counselling is an integral part of HIV testing

The first consultation

The first meeting between the HIV-infected person and the healthcare provider is of utmost importance because it establishes a relationship and, hopefully, partnership that may last for many years. It should therefore be regarded as an opportunity to begin developing a mutually beneficial relationship as well as an opportunity to collect clinical information. The

initial assessment of the HIV-infected person should include: (i) a comprehensive clinical history, (ii) a thorough physical examination and (iii) the taking of samples for laboratory tests to provide information that enables the clinician to:

- Stage the HIV infection
- Diagnose any associated conditions
- Review the need for counselling, education and psychosocial support
- Plan follow-up care and immunisations
- Consider the implications for and, when appropriate, plan the initiation of ART
- Consider the implications for, and, where appropriate, initiate prophylactic therapy

The clinical history and physical examination

The clinical assessment is concerned with symptoms and signs, previous medical history and also the risk assessment including other contributing lifestyle issues. The time devoted to the noting of signs and symptoms should initially focus on the most common HIV-related symptoms. However, any more unusual signs or symptoms reported proactively by the patient should be followed up.

The physical examination performed on all patients at the time of the first encounter should be as comprehensive as possible. The skin, oropharynx and lymph nodes will require examination in virtually all cases. Particular attention should be paid to the examination of the skin because dermatological manifestations are among the most common early manifestations of HIV infection. The oropharynx should also be carefully examined because many manifestations of HIV infection affect mucous membranes. Common HIV-related mucocutaneous conditions are presented in Figures 1-5. Generalised lymphadenopathy is common among HIV-infected patients. Examinations of other parts of the body, such as the anogenital region, nervous system and eyes will be necessary in many cases. Anogenital examination should be performed whenever reasonably possible to assess for signs of sexually transmitted diseases and other manifestations of HIV infection that affect mucous membranes. Cognitive function should initially be assessed as part of a generalised neurological examination, but more sensitive neuropsychological testing is appropriate in cases where dementia is suspected. Ophthalmic examination should form part of the generalised neurological examination.

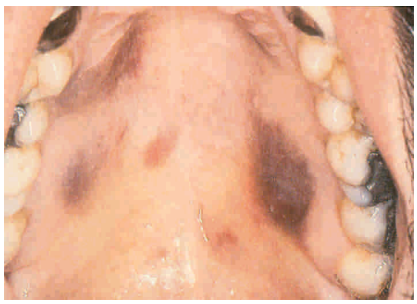

Figure 1: Hyperpimented lesions in oral cavity due to Kaposi's sarcoma, which is caused by infection with human herpes virus-8 (HHV-8)

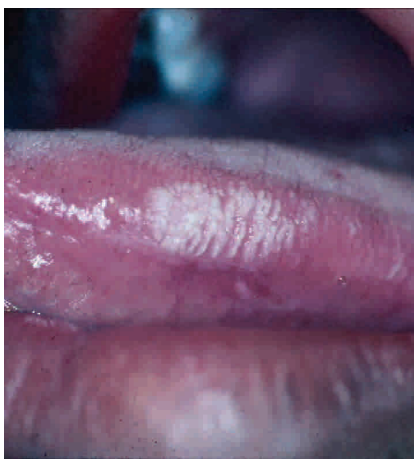

Figure 2: Shiny white discolouration on the side of this HIV-infected patient's tongue due to oral hairy leukoplakia (OHL) caused by infection with Epstein-Barr virus (EBV)

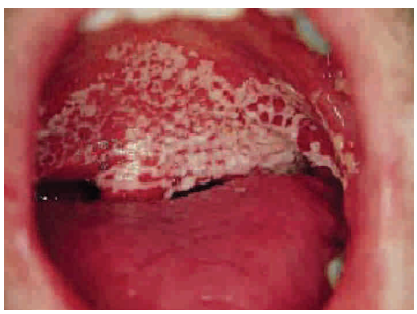

Figure 3: Pseudomembranous form of oral thrush caused by *Candida albicans*

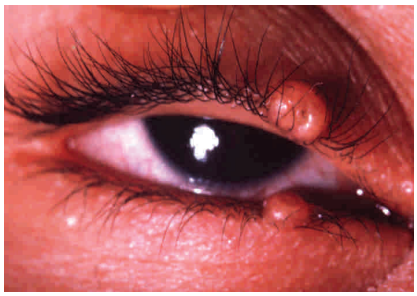

Figure 4: Aymptomatic and painless umbilicated papules due to molluscum contagiosum, which is caused by infection with the pox virus

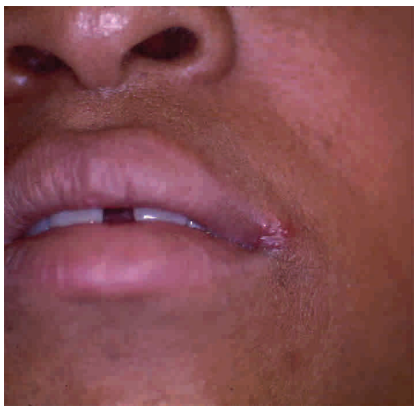

Figure 5: Herpes simplex virus-1 (HSV-1) infection causes painful vesicular lesions

Laboratory diagnosis of HIV infection

In South Africa, serological testing for anti-HIV antibodies is currently recommended for the diagnosis of HIV infection.[3,4] Although the diagnosis of HIV can also be made by the detection of viral antigens such as p24 (the core protein of the virus), the detection of viral nucleic acid by polymerase chain reaction (PCR), or by isolating the virus in cell (lymphocyte) culture, assays based on the detection of antibodies to the antigens of HIV are most commonly used in the form of Enzyme Linked Immunosorbent Assay (ELISA).[3,4] In areas with a high seroprevalence of HIV infection (prevalence > 5%), the Global Programme on AIDS of the World Health Organisation suggests that multiple ELISA's can be used to accurately determine the HIV status of an individual. Most rapid tests are applications of the ELISA principle, and some of the rapid tests are highly respected and feature amongst the top bench ELISA's in their accuracy. According to WHO guidelines, on site testing can be done using two

different types of rapid tests. The blood is obtained through a finger prick. On site testing has the advantage of a quick turn around time for results and the patient can be given his/her result almost immediately. This may be particularly useful in a group of patients who may not return for their results. Pre-test counselling is regarded as a prerequisite to performing an HIV test, including rapid tests. The patient must give his/her response to the test and persons doing the test without the patient's consent are liable for prosecution.[5]

Whilst multiple ELISA testing has been used in developing countries (including South Africa), the most widely used confirmatory test for HIV infection in most developed countries is a qualitative HIV DNA polymerase chain reaction (PCR) for detection of viral particles in the plasma or the Western blot test. (Table 3.) The Western blot assay is very labour intensive, relatively expensive and sometimes gives indeterminate results.[3,4] The HIV DNA polymerase chain reaction test is a qualitative molecular assay that determines whether HIV is present in the blood. It is reported as positive or negative and needs to be distinguished from quantitative HIV RNA PCR assays that determine the viral load (amount of HIV RNA in the blood) and is expressed as the number of HIV RNA copies per millilitre (RNA copies/ml) or the logarithmic equivalent – $\log_{10}$ equivalent.[6]

Window period

Tests detecting the actual viral particle will become positive before the antibody response due to the virus appearing in the peripheral blood in its early replication cycles (viraemia) before serocoversion occurs. In this phase of infection, the levels of virus detectable (the viral load) may be very high. Current experience puts the antibody window period utilising the latest generations of antibody tests in most (but not all) cases at about 21-24 days and this is compatible with our understanding of the pathogenesis of generalised viral infections. After the immune system responds, the viral load typically drops considerably to reach a steady state (the set point) and will remain at this level characteristic for a given individual for a number of years.

Insurance testing

In situations where healthy individuals are screened, such as in insurance testing, the pre-test likelihood may be much less predictable because of the clustering of groups with different HIV prevalence. Confirmatory testing assumes more importance and there are typically protocols in place to handle insurance testing. However, the direct involvement of a knowledgeable clinician in cases where false positive results have emerged would considerably ameliorate the associated difficulties and suffering.

Special considerations in the newborn

Infants born to HIV-infected women can test positive in serological (antibody) tests for HIV up to 18 months following birth, due to the transfer of maternal antibodies across the placenta. Beyond this age, however, only truly HIV-infected children test positive for HIV in ELISA and Western blot assays. In the absence of hypogammaglobulinemia, infants who revert to being negative for HIV antibodies after 12 months of age are not infected with HIV.

Most HIV-infected infants can be diagnosed during the first month of life, often before the development of any HIV-related symptoms.[7] The most important laboratory investigation for this is PCR to detect HIV DNA in peripheral blood mononuclear cells. Due to the risk of contamination with maternal blood, infant blood samples taken for diagnostic evaluation should not be collected from the umbilical cord blood and furthermore, the sensitivity of PCR is not good in the first week of life. This is probably a reflection of the importance of perinatal transmission as the main means by which an infant acquires infection. An infant born to an HIV-infected mother is considered uninfected if PCR results are persistently negative until > 4 months of age in the absence of breastfeeding.[7]

Tests for additional clinical information

Several laboratory tests should be performed in patients with serologically confirmed HIV infection. These include quantitative HIV RNA measurement (how actively is the virus replicating?), CD4+ cell count (how far is the immune system compromised?), complete blood count and chemistry, tests for certain sexually transmitted diseases (RPR) as well as other infectious diseases. False-positive tests for syphilis are common, but can be excluded by use of a confirmatory FTA test.

Table 3: Indications for the use of qualitative HIV DNA PCR testing

- Determine HIV infection in infants under the age of 18 months born to HIV infected mothers
- Determine HIV infection in abandoned or orphaned infants under the age of 18 months who are HIV ELISA positive
- Early determination of infection in sexual assault or rape cases
- Early determination of infection after occupational exposure, such as needle stick injuries or mucosal contamination
- Determine HIV infection in blood or organ donors

Table 4: Relationship between CD4+ cell counts and immune function

CD4+ cell count (cells/µl)	**Immune function**
> 500	Relatively normal immune function
350 – 499	Moderate immune suppression
200 – 349	Moderately advanced immune suppression
50 – 199	Advanced immune suppression
< 50	Severely advanced immune suppression

Appropriate gynaecological tests (cervical smear) are also useful for female patients. It is, however, important to approach all aspects of management with a view to optimising the outcome for the patient including the costs. The decision to implement antiretroviral treatment requires a comprehensive view including the all-important assessment of the adherence profile of a given patient.

Evaluating the degree of immune dysfunction

HIV causes gradual but progressive immunodeficiency and measurement of the immune status of the patient has become central to HIV management. The most important cell involved in the immune attrition is the CD4+ T-lymphocyte as it has a co-ordinating and central role in the immune response.[8] Derangements occur involving other components of the immune system, both humoral and cellular, but the level of CD4+ cells in the peripheral blood is the key parameter to use in monitoring the changes. It has an invaluable role in staging HIV infection, establishing the risk of specific HIV-associated complications, determining the need for prophylaxis against opportunistic infections and assessing responses to antiretroviral therapy. In adolescents and adults, normal CD4+ cell counts vary between 700 and 1100 cells per microlitre (µl) blood. In HIV infected adults, CD4+ counts will usually fall by 40-80 cells/µl/year. The CD4+ cell count is a relatively good surrogate marker for immune function as presented in Table 4. In infants and children, CD4+ cell numbers may exceed 2000 cells/µl and are likely to fall much more rapidly due to the higher viral load in children who have a less developed immune system, which is less effective in combating HIV. In children, CD4+ cell counts are usually expressed as a percentage of the lymphocyte count (CD4%). The CD4% is less subject to variation on repeated measures.

Full blood count and serum chemistry

A complete blood count should be obtained to check for anaemia, leukopenia and thrombocytopenia, which are all common in HIV-infected individuals, to facilitate calculation of the absolute CD4+ cell count and to provide baseline data prior to the initiation of potentially myelo-suppressive therapy. Blood chemistry should also be assessed to provide information on the patient's nutritional status, renal function and hepatic function (transaminases), and to provide baseline data prior to the initiation of potentially hepatotoxic therapy. In patients who have deranged liver function tests, further tests should be considered to exclude hepatitis B and hepatitis C.

Follow-up visits

Follow-up has to be arranged to discuss the results and plan the further management of the patient. The diagnosis of HIV impacts not only on the infected individual, but has far reaching consequences for his/her family, partner and friends. The patient needs to receive as much relevant information as possible about the condition, but also a supportive environment in which a doctor-patient partnership can grow. The counselling process is ongoing, there are no quick answers and the physician must assist his/her patient to develop coping skills.[9,10]

See CPD Questionnaire, page 34

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