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CPD QUESTIONS

Journal 38

Two CPD points are awarded for the correct completion and submission of the questions below.

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This programme is available free of charge to members of the HIV Clinicians Society and SAMA only.

1. True (A) or false (B) – click on the correct answer:
   The immune reconstitution syndrome (IRIS) typically occurs late in antiretroviral therapy.

2. True (A) or false (B) – click on the correct answer:
   IRIS is a typical manifestation of antiretroviral therapy (ART) commencement in early HIV infection in pregnant women.

3. True (A) or false (B) – click on the correct answer:
   Cryptococcal meningitis is a serious IRIS manifestation.

4. True (A) or false (B) – click on the correct answer:
   In regions where highly active antiretroviral therapy is offered in pregnancy regardless of maternal CD4 count, vertical HIV transmission has almost disappeared.

5. True (A) or false (B) – click on the correct answer:
   TB colitis may be an extrapulmonary complication of HIV/TB co-infection.

6. True (A) or false (B) – click on the correct answer:
   Abdominal ultrasound is a useful investigation in HIV patients with abdominal symptoms.

7. True (A) or false (B) – click on the correct answer:
   Non-tuberculous mycobacterial infection is only seen in patients with well-preserved immunity.

8. True (A) or false (B) – click on the correct answer:
   Soluble transferrin receptor levels are low in patients with iron deficiency anaemia.

9. True (A) or false (B) – click on the correct answer:
   Transferrin levels are usually low in anaemia of chronic disorders.

10. True (A) or false (B) – click on the correct answer:
    Mycobacterium avium complex is a non-tuberculous mycobacterial infection that occurs most commonly in the duodenum in gastro-intestinal infections.

11. True (A) or false (B) – click on the correct answer:
    Pneumocystis jirovecii is an important protozoal opportunistic infection in HIV.

12. True (A) or false (B) – click on the correct answer:
    The Grocott-Gomori methamine-silver stain is useful for identifying non-tuberculous mycobacteria.

13. True (A) or false (B) – click on the correct answer:
    Treatment for *P. jirovecii* may involve atovaquone.

14. True (A) or false (B) – click on the correct answer:
    South Africa has a Traditional Health Practitioners Act (No. 22 of 2007) that requires registration by traditional healers.

15. True (A) or false (B) – click on the correct answer:
    In the study discussed in this journal, most traditional healers kept careful records of each of the treatment packages they prepared themselves.

16. True (A) or false (B) – click on the correct answer:
    A person engaging in potentially high-risk sexual activity as indicated on the South African National Blood Service questionnaire is deferred from blood donation for 6 months.

17. True (A) or false (B) – click on the correct answer:
    South Africa is a country where men who have sex with men may not donate blood.

18. True (A) or false (B) – click on the correct answer:
    Tablet returns may be a potential way of introducing adherence conversations with patients on ART.

19. True (A) or false (B) – click on the correct answer:
    A haemoglobin level below 8 g/dl in an HIV-infected patient is probably due to anaemia of chronic disorders.

20. True (A) or false (B) – click on the correct answer:
    The Ziehl-Neelsen stain will show intracellular acid-fast bacilli in an *M. avium* complex infection.

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CASE STUDY

PNEUMOCYSTIS JIROVECII INFECTION OF THE EXTERNAL AUDITORY CANAL

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Pneumocystis jirovecii is well known to cause interstitial plasma cell pneumonia in immunocompromised patients. It has been implicated as a rare cause of infections in other anatomical sites.[1] We report a rare case of *P. jirovecii* infection of the external auditory canal. This was the first manifestation of a previously unknown HIV infection.

CASE REPORT

A 27-year-old man was referred to the ENT clinic with a mass in the right external ear canal. He had no past medical history of note. Presenting symptoms included bloody otorrhoea, otalgia and decreased hearing in the right ear for 2 months. On examination the presence of a large polyp was confirmed. The tympanic membrane could not be visualised owing to the size of the polyp. The left ear appeared normal. The biopsy showed inflamed, partly necrotic granulation tissue, reported as a pyogenic granuloma. A trial of steroid-antibiotic ointment was commenced.

The patient's symptoms persisted, and he was booked for an examination under anaesthesia. Clinically he was pyrexial, with worsening otitis externa and a recurring polypoid mass formation with large, pale granulations. Biopsy resulted in profuse bleeding. The differential diagnosis was tuberculosis or glomus tympanicum. Laboratory investigations revealed an erythrocyte sedimentation rate of 60 mm/h but a normal peripheral white cell count. He had no clinical evidence of pulmonary disease and a chest radiograph appeared normal. There was no other apparent source of infection. Histological examination revealed an acute inflammatory response with no granulomas, and a Ziehl-Neelsen stain was negative. An HIV test showed the patient to be HIV infected. Anti-tuberculosis (TB) medication was commenced empirically and a repeat biopsy was taken. The patient's pyrexia resolved and he was subsequently discharged.

The patient was lost to follow-up and presented again 3 months later. A necrotic polyp occluding the external ear canal was still evident. Biopsy taken at the previous presentation suggested a possible cholesteatoma. All specimens sent for TB culture were negative. The CD4 count from the previous admission was 24 cells/µl. An urgent temporal bone computed tomography (CT) scan revealed opacifications in the middle ear and mastoid cavity with the ossicles and scutum still intact, making the diagnosis of cholesteatoma less likely. The most recent biopsy showed granulation tissue, suppurative inflammation, focal giant cells, fibrin and copious amounts of foamy exudates. Special stains were performed to exclude other pathologies. Ziehl-Neelsen and Brown and Brenn stains were again non-contributory, but a Grocott-Gomori methenamine-silver stain (Fig. 1) showed the presence of *Pneumocystis* cysts confirming a diagnosis of otic pneumocystosis. The patient was commenced on high doses of oral trimethoprim-sulfamethoxazole and referred to the HIV clinic for initiation of highly active antiretroviral therapy. During a telephonic conversation 2 months later he reported symptomatic improvement. The otorrhoea and pain had subsided but he still had hearing loss.

DISCUSSION

Pneumocystis jirovecii infection is an important opportunistic infection. The organism was discovered in 1909 by Chagas, but the cystic forms were mistakenly considered to be part of the trypanosome life cycle. It was named *P. carinii* (Greek: *pneumon* 'lung', *kystis*

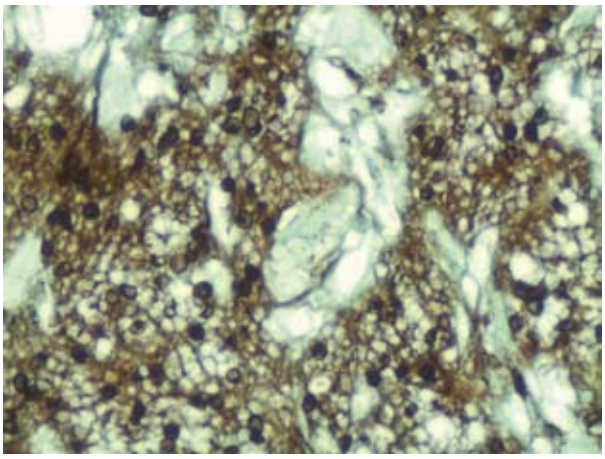

Fig. 1. Grocott-Gomori methenamine-silver stain showing Pneumocystis *cysts of variable shape and size (40 × magnification).*

'cyst').[2] Until 1988 the organism was considered to be a protozoan. The controversy regarding its taxonomy and classification continued for decades and recently, based on ribosomal RNA homologous to that found in fungi,[2] it was re-classified as a fungus. Advances in molecular technology led to *Pneumocystis* organisms infecting humans being re-named *P. jirovecii* in 1999.[3]

P. jirovecii infection is an important opportunistic infection, and the incidence of pneumocystis pneumonia is on the increase in sub-Saharan Africa. Extrapulmonary pneumocystosis is, however, a rare complication and represents less than 1% of all cases of infection.[4] One or more tissue or organ sites may be involved, with the most common being lymph nodes, bone marrow, spleen and liver. Otic pneumocystosis is exceedingly rare. It has only been described in the past 2 decades, and up to 2008 only 14 cases had been reported in the English literature.[3]

It is postulated that under favourable conditions extrapulmonary dissemination can occur via the lymphatic and haematogenous routes.[4] One theory is that these individuals may have more virulent strains. Observations in rat models suggest that heavy organism load and destruction of lung tissue may contribute to extrapulmonary dissemination.[5] Conversely, *P. jirovecii* infection may be a systemic disease that most commonly affects the lungs. Extrapulmonary infection becomes more evident when prophylaxis is focused on the respiratory tract, and this may explain the correlation with the use of aerosolised prophylactic pentamidine.[1,4]

Although the mechanism of primary otic pneumocystosis is as yet unclear, it has been suggested that it may follow airborne invasion by trophozoites of the external auditory canal[6] and that the middle ear may become involved after spread from nasopharyngeal carriage via the eustachian tube.

Individuals with otic pneumocystosis may have nonspecific symptoms of otorrhoea, otalgia, hearing loss, vertigo and tinnitus. Clinical findings include a mass in the external auditory canal and occasional otitis media. Destruction of the ossicles and sclerosis of the mastoid air cells, extensive bony erosion, and extension into the middle cranial fossa are rare complications documented in the literature.[3]

Diagnosis can be confirmed by biopsy, which is essential to rule out malignancy or other infective pathogens.[6] Organisms can be demonstrated on microscopic examination of tissue sections and cytological preparations using silver, fluorescent or immunoperoxidase staining methods. The standard method using a Grocott-Gomori methenamine-silver stain is easy and reliable. Cystic forms are round to oval, 4 - 7 µm in dimension, and appear as collapsed crescent- or helmet-shaped forms. The granulomatous reaction is composed of trophozoites and cysts, which appear as basophilic dots on H&E. There is a variable inflammatory infiltrate.

As for pulmonary pneumocystis, medical therapy consists of oral or intravenous trimethoprim/sulfamethoxazole. Other regimens described include dapsone/trimethoprim, clindamycin/primaquine, atovaquone and pentamidine isethionate.[1,3] Although there is usually resolution of symptoms after medical therapy, surgical excision of lesions in the external auditory canal may be clinically indicated.

Disseminated pneumocystosis, like *Pneumocystis* pneumonia, has high mortality rates. The prognosis may be better for those with single extrapulmonary site involvement and no concomitant lung infection.[4] It is important for health care professionals to be aware of this infection as the HIV pandemic continues and results in common infections manifesting in extraordinary ways and in unusual sites.

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CASE STUDY

A RARE PHENOMENON OF ATYPICAL LIPODYSTROPHY IN A PATIENT ON HAART IN THE ABSENCE OF A PROTEASE INHIBITOR REGIMEN

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Lipodystrophy is a complication of patients on antiretroviral (ARV) medication; however, it is commonest in patients on long-term treatment and those on protease inhibitor (PI) regimens.[1,2] We present a rare case of atypical lipodystrophy, presenting as multiple subcutaneous lipomas, in a patient who had been on a non-PI ARV regimen for 6 weeks.

CASE HISTORY

A 45-year-old man, known to be hypertensive and with a history of smoking (5 cigarettes a day for 18 years), presented to Tygerberg Hospital with peripheral vascular disease necessitating bilateral amputations at the knee. The patient had no other significant medical disorders and no previous history of tuberculosis (TB), and consumed alcohol socially. He had been well before this admission, with no previous medical or surgical admissions. The findings on general and systemic examination were normal and no lumps were noted on the body.

The patient was tested for HIV as part of his surgical work-up and was found to be positive with a CD4 count of 152 cells/µl. He was commenced on ARVs: stavudine (D4T) 30 mg 12-hourly, lamivudine (3TC) 150 mg 12-hourly and efavirenz (EFV) 600 mg at night. He underwent successful above-knee amputations and was subsequently followed up at the Tygerberg Hospital Infectious Disease Clinic approximately 1 month later.

The patient was doing well and reported no problems or side-effects from the ARVs. The stumps were clean and findings on a thorough physical examination were normal. No lumps were detected on the patient's body at this visit. The patient had no symptoms of TB, but a chest radiograph revealed infiltrates in the right upper zone. At this stage we were still awaiting sputum results from his initial admission. Two weeks later (approximately 6 weeks after ARV initiation) drug-susceptible TB was diagnosed on sputum culture. TB treatment was immediately commenced.

The patient returned for a follow-up visit after a further 2 weeks complaining of multiple lumps on the trunk and abdomen. Physical examination revealed multiple soft, mobile, non-tender nodules on the abdomen (Fig. 1), measuring approximately 2×2 cm. A fine-needle aspirate and excision biopsy confirmed that these were lipomas. A fasting lipogram revealed a total cholesterol level of 5.7 mmol/l, a triglyceride level of 2.0 mmol/l, a high-density lipoprotein (HDL) cholesterol level of 1.2 mmol/l and a low-density lipoprotein (LDL) cholesterol level of 3.6 mmol/l.

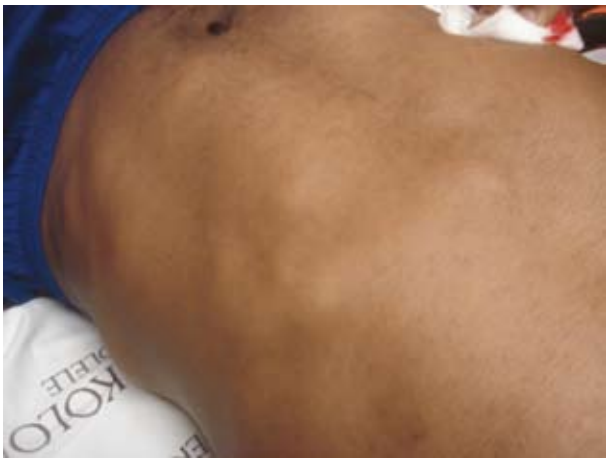

Fig. 1. Multiple lipomas on the patient's abdomen.

The patient was counselled regarding his condition and continued on his anti-TB treatment and ARVs. He was started on the appropriate medical management for his dyslipidaemia and given appropriate dietary advice.

DISCUSSION

Lipodystrophy encompasses both lipo-atrophy and lipohypertrophy. Lipo-atrophy presents as subcutaneous fat wasting in the face and peripheries, whereas lipohypertrophy occurs as fat accumulation in the abdomen, breast and dorso-cervical region.[2,3] Lipodystrophy can be associated with hyperlipidaemia and insulin resistance, which constitute the lipodystrophy syndrome.[3] The commonest class of ARVs to cause lipodystrophy is the PIs.[1-3] These agents are commonly used in second-line regimens in ARV treatment in South Africa.

This patient presented with multiple subcutaneous lipomas on the abdomen 6 weeks after commencing ARVs and approximately 2 weeks after starting TB treatment. This was an extremely interesting and yet perplexing presentation. Diagnosis of a novel immune reconstitution inflammatory syndrome phenomenon or a cutaneous lymphoma was considered, but the patient was clinically well, histological examination confirmed a lipoma with no inflammatory cell infiltrate, and biopsies of the lesions did not culture TB or any other bacterial organism.

The reason for the acute onset of the lipomas, and in a patient not on a PI, eludes the authors. The patient's background medical condition of hypertension and peripheral vascular disease may have contributed to the development of the lipomas. Google Scholar and Pubmed searches in the English language revealed only 1 other case in which subcutaneous lipomas developed on a regimen without PIs.[4] That patient had been on 3TC, tenofovir and EFV. It is unclear whether EFV, 3TC or both contributed to the lipomas in our case, as that patient was also on both these agents.

Most patients who develop lipodystrophy syndrome while on PIs are switched to a non-nucleoside reverse transcriptase inhibitor, usually with improvement in their dyslipidaemia.[4,5] Owing to the unique nature of our case, with no evidence base to guide treatment, it was decided to continue the regimen of 3TC, D4T and EFV.

It is important that clinicians are aware of this rare and atypical form of lipodystrophy, which can apparently occur in patients taking nucleoside reverse transcriptase inhibitors and non-nucleoside reverse transcriptase inhibitors. If it occurs, the most important issue is to counsel the patient regarding lipomas and their benign nature and that they should remain compliant on treatment. It would be useful if a registry could be created to document such atypical adverse effects of ARVs in order for research to be conducted which may prevent such phenomena and guide us on appropriate drug changes if and when required.

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CASE STUDY

A CASE OF PALATAL PERFORATION CAUSED BY TOXOPLASMOSIS

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We describe the case of a 35-year-old HIV-positive man seen at the Infectious Diseases Institute, Kampala, Uganda, with a 2-week history of palatal perforation.

HIV infection has several oral manifestations, including oral candidiasis and oral hairy leucoplakia. Occasionally unusual presentations requiring rigorous investigations are seen, and in these cases the diagnosis sometimes remains a dilemma owing to limited investigation facilities.[1-3] We present the case of a patient who presented with a puzzling oral lesion.

CASE HISTORY

A 35-year-old HIV-positive man first presented to the Infectious Diseases Institute, Kampala, in 2006. He had World Health Organization (WHO) stage IV disease with a history of oesophageal candidiasis, a baseline weight of 58 kg and a CD4+ count of 56 cells/µl. He was initiated on highly active antiretroviral therapy (HAART) using a combination of stavudine, lamivudine and nevirapine (Triomune-30) together with co-trimoxazole prophylaxis.

Six months after initiating ART, a follow-up CD4+ count had risen to 226 cells/µl. Subsequently the count rose to 298 cells/µl.

In September 2008, the patient presented with a 4-month history of drenching night sweats and high-grade fevers, his temperature being recorded as 39.3°C and 39.7°C on two occasions. There was no history of cough, weight loss or loss of appetite. The results of investigations at this time were as follows: full blood count – leucocytopenia, 1.1×10^3/l ; ESR – 25 mm/h; blood slide for malaria parasites – none seen; urinalysis – normal; chest radiograph – normal; abdominal ultrasound scan – hepatosplenomegaly with a suggestion of a haemangioma in the liver; serum cryptococcal antigen – negative; blood cultures – no bacterial growth after 7 days of incubation; TPHA – non-reactive.

On the basis of the unrelenting fever the patient was started on tuberculosis (TB) treatment consisting of rifampicin, isoniazid, ethambutol and pyrazinamide. During this time his antiretroviral therapy was switched to zidovudine, lamivudine and efavirenz.

Two weeks after the start of TB treatment, the patient developed drug-induced hepatotoxicity and the TB treatment was stopped. A week later difficulty in swallowing and marked weight loss were noted. He was treated with fluconazole and acyclovir for a month with no improvement, at which time he was admitted.

Two months after stopping TB medication the liver enzymes stabilised and he was restarted on anti-TB medication.

In January 2009, the patient presented with a 3-week history of high-grade fever, loss of appetite, cervical lymphadenopathy and a 2-week history of pus discharge from a palatal perforation, which was treated with ceftriaxone and fluconazole (Fig. 1).

Fig. 1. Perforation of hard palate.

An ENT consultation gave a presumptive diagnosis of histoplasmosis and the patient was initiated on amphotericin B.

The results of investigations at this stage were as follows: oral fistula swab – 2+ yeast cells, 2+ Gram-positive cocci and 3+ Gram-negative rods; no inflammatory cells seen. A complete blood count showed macrocytosis and mean corpuscular volume of 103 fl; CD4+ count (13 January) – 71 cells/µl (this was less than half the peak CD4+ count, prompting measurement of viral load to exclude immunological failure); viral load (13 January) – not detected, with a lower limit of detection of 400 copies; lymph node aspirate – polymorphonuclear leucocytes 3+, Gram-negative rods 2+, Gram-positive cocci 1+, no acid- and alcohol-fast bacilli seen, *Escherichia coli* isolated; lymph node biopsy – fibrosis and chronic granulomatous inflammation with central necrosis and epitheloid cells, small organisms with halo extracellular and within-macrophage cytoplasm. Morphological features were consistent with toxoplasma lymphadenitis (Fig. 2).

The patient did not return to the Institute. The first follow-up phone call (within a week) revealed that he was deteriorating and was too weak to come to the clinic, and when we called the next week we were told that he had died. Unfortunately, the histopathology results were only obtained after his death.

DISCUSSION

This case is an example of the rare oral lesions seen in HIV-infected patients in our clinic. We comprehensively reviewed the literature on bone and joint disease in association with HIV infection but did not find a case of toxoplasma-related bone disease. Toxoplasma infection of the oral cavity is uncommon.[4] A case of intra-oral lymphadenitis secondary to toxoplasmosis has however been reported.[4]

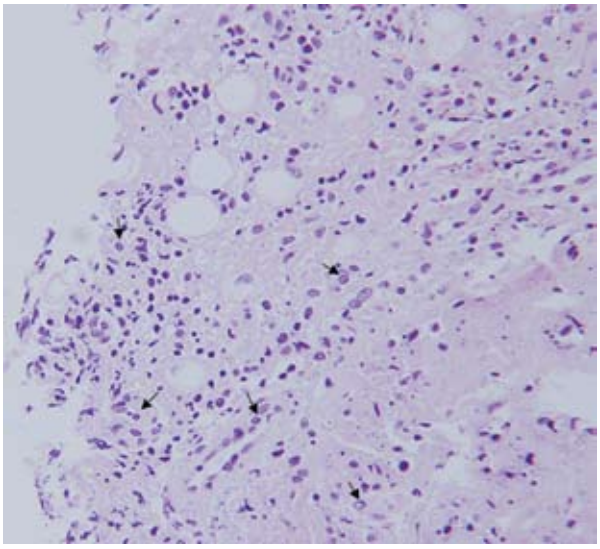

Fig. 2. Intracellular organisms with prominent outlines indicated by arrows.

In our case defective cell-mediated immunity as a result of immunosuppression may have facilitated the rapid dissemination of toxoplasma,[5] resulting in bone invasion causing bone disintegration and destruction.[5]

Acknowledgement: Dr Robert Lukande, Histo-pathologist, College of Health Sciences, Makerere University.

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CASE STUDY

TUBERCULOUS ABDOMINAL ABSCESS IN AN HIV-INFECTED MAN: NEITHER INFECTION PREVIOUSLY DIAGNOSED

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A 38-year-old man had a 1-week history of right lower quadrant abdominal pain; the initial impression was that he had diverticulitis of the ascending colon with an intra-abdominal abscess. Signs of peritonitis mandated an immediate right hemicolectomy. The unusual location of the abscess and the patient's unusual postoperative course suggested that he might also have a systemic disease. Testing for HIV infection was positive. After 2 weeks in hospital, he was treated as an outpatient for both tuberculosis and HIV with a favourable outcome.

In Taiwan a pre-operative HIV test is not performed routinely, and the HIV seroprevalence in surgical patient populations is unknown. Surgeons should keep the possibility of HIV infection in mind in a patient with an unusual clinical course.

The number of new cases of human immunodeficiency virus (HIV) infection in Taiwan peaked in 2005, and it is still a serious problem.[1] Tuberculosis (TB), especially extrapulmonary TB, is also common in Taiwan[1] and is commonly associated with HIV infection.[2] When a patient urgently needs surgery, as can occur with perforation of an intestine or appendix, there is no time for definitive testing for HIV and/or TB.

We report a case in which a patient required immediate surgery for what appeared to be an abscess with peritonitis from a perforated diverticulum of the ascending colon. The patient was unaware that he had both extrapulmonary TB and HIV. The TB was discovered by the pathologist on examination of the surgical specimen, and the HIV was discovered because the patient's postoperative condition suggested a systemic disease. The case illustrates that despite co-occurrence of the two diseases surgery can be successful, recovery can be similar to that expected in a patient without the diseases, and patient outcome can be good if anti-TB and antiretroviral therapies are started almost immediately. The case is also consistent with previous reports that patients with HIV undergoing surgery have similar conditions to HIV-negative patients and that the results of treatment are equivalent.[3]

CASE REPORT

A 38-year-old man who had been well without systemic disease and neither drank alcohol nor smoked had experienced dull, right lower quadrant abdominal pain for 1 week, and fever with chills for 2 days. He had no other associated symptoms such as nausea, vomiting or diarrhoea. He sought help at the emergency department, where physical examination showed rebound tenderness at the right lower quadrant of the abdomen, with muscle guarding and rigidity. The white blood cell count was 8×10^9/l, with 11% band-form neutrophils. An elevated C-reactive protein level (5.77 mg/dl) was noted. After he was admitted on 29 April 2006, an abdominal computed tomography scan revealed an ill-defined mass in the right lower quadrant anterior to the right psoas muscle; it was suspected to be an abscess. There were also several small abscesses in the omentum, paracolic gutter and mesentery of the ascending colon (Fig. 1). The clinical impression was that he had perforated diverticulitis with intra-abdominal abscess, and he was immediately operated on. At surgery the abscess was found to be at the ascending colon mesentery. A right hemicolectomy was performed because of the high level of suspicion of a perforated diverticulum (Fig. 2). Postoperatively, the patient had a high fever for 3 days even with intensive treatment with a second-generation cephalosporin (cefmetazole 1 g 8-hourly). A systemic disease was suspected because the unusual clinical profile, including the location of the abscess and the pathological findings, did not correspond with the patient's general condition. HIV infection was considered, and a Western blot test was positive for HIV. The patient's CD4 cell count, measured by flow cytometry, was 306/µl, and his CD8 cell count was 677/µl. The HIV viral load was measured by indirect enzyme-

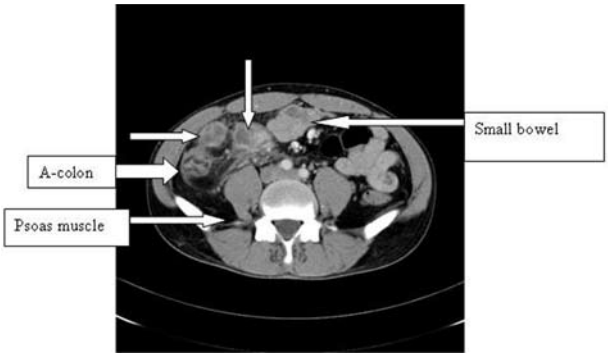

Fig. 1. Pre-operative computed tomography scan of the abdomen. The largest abscess is located at the ascending colon mesentery, anterior to the right psoas muscle (vertical arrow). There are several smaller abscesses over the omentum, and paracolic gutter (horizontal arrow).

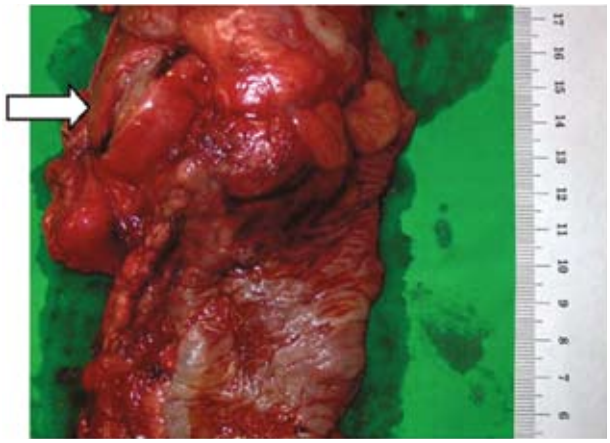

Fig. 2. The largest abscess after excision. This abscess was found adjacent to the ascending colon (arrows).

linked immunosorbent assay (ELISA) and found to be 6 790 copies/ml.

The final diagnosis was HIV infection coincident with the histologically confirmed *Mycobacterium tuberculosis* colitis and abscess formation. Anti-TB drugs (rifampin + ethambutol) were started soon after the patient resumed oral intake. He was discharged on 11 May 2006, 14 days after admission, at which time highly active antiretroviral therapy (HAART) was started, including abacavir, efavirenz and lamivudine. Anti-TB drugs were given continuously in the outpatient department for 18 months; the regimen included isoniazid, rifampin, ethambutol and pyrazinamide. The patient was followed up until August 2009 with a favourable outcome; at that visit he had a viral load of <400 copies/ml, a CD4 count of 332 cells/µl and a CD8 count of 632 cells/µl.

DISCUSSION

Our patient was unaware that he had TB and HIV infection, and because he urgently needed surgery we did not have time to perform laboratory tests to diagnose these infections. Nevertheless, he quickly recovered from the surgery and was discharged from the hospital 2 weeks after admission. Outpatient treatment for the TB and HIV had a favourable outcome.

TB has become a major cause of death and disability in many parts of the world, especially in developing countries.[4,5] The disease can affect almost any body system, although most cases are pulmonary.[6] In the USA, cases of extrapulmonary TB increased from 13.5% of all reported TB cases in 1975 to 21.0% in 2006.[7] A study in Taiwan found that extrapulmonary TB cases increased from 23% to 27% from 1996 to 2003.[8] Abdominal TB is a rare manifestation of extrapulmonary TB, with a prevalence of around 3%.[6] It may involve the gastro-intestinal tract, peritoneum, mesenteric lymph nodes, genito-urinary tract, or other solid organs.[4,6,9]

Abdominal tuberculosis frequently poses a diagnostic challenge because specimens may be difficult to obtain, and the concentration of organisms may be low. Sanai and Bzeizi compiled data from 39 studies and found that the sensitivities of various diagnostic tests in patients with TB peritonitis were 38% for an abnormal chest radiograph and 53% for a positive purified protein derivative test.[10] Examination of ascites fluid found that lymphocytes predominated in 68% of cases, and that there was an elevated lactate dehydrogenase level in 77% of cases and an elevated adenosine deaminase level in 84%. Mycobacteria were found in 34% of ascites fluids on culture, but only 3% of examinations detected organisms by smear. In contrast, the sensitivity of laparoscopic diagnosis was 92%.[10] These diagnostic tests for abdominal TB seem unreliable, partly because not every patient develops ascites. Culture of ascites fluid or peritoneal biopsy is the gold standard test. However, even a final diagnosis of pulmonary TB usually takes considerable time; diagnosis of abdominal TB typically takes even longer.

One study from the National Taiwan University Hospital demonstrated that the mean interval between the first day of admission and respiratory isolation for pulmonary TB was 20.5 days.[11] On the other hand, Bernhard *et al.* reported that physicians considered abdominal TB in the initial differential diagnosis in only 39% of cases (7/18). Time to specific diagnosis ranged from <1 week to >3 months.[12] Chen *et al.* reported that the average time to diagnosis of abdominal TB in southeastern Taiwan was 48±10 days.[13] Delay in the diagnosis of abdominal TB is therefore more common than for pulmonary TB.

Several studies have observed that the proportion of extrapulmonary TB is higher in individuals who also are infected with HIV[14,15] and in foreign-born immigrants[16] in the USA. In addition, a dramatically increasing TB notification rate was observed in sub-Saharan Africa between 1990 and 2005, especially in countries with a high prevalence of adult HIV (>5%).[17] *The International Standards for Tuberculosis Care* states that HIV counselling and testing is indicated for all patients with TB in areas with a high HIV prevalence.[18] In Taiwan, 15 011 cases of HIV infection had been reported to the

Taiwan Centers for Disease Control as of 31 December 2007.[1] The case burden of HIV infection in Taiwan is significantly lower than that of TB. More data are required to establish the cost-effectiveness of offering HIV testing to TB patients in a region of high TB and relatively low HIV prevalence, such as Taiwan.

We describe this rare case to alert physicians to the fact that with the current trend of increasing HIV prevalence among the Taiwanese, HIV co-infection should be considered when extrapulmonary TB is suspected.

Medical treatment is preferable to treat abdominal TB in patients also infected with HIV, surgery being reserved for complications such as intestinal obstruction, fistula, perforation and haemorrhage.[19] Our patient was operated on because he had abscesses and peritonitis, which were a complication of TB colitis. With the availability of the surgical specimen, we followed our suspicion and diagnosed HIV, enabling prompt initiation of treatment. Anti-TB medication was started within 10 days, and the patient was discharged in 14 days. The course of diagnosis and treatment was straightforward. After discharge he received medical treatment as an outpatient with a favourable outcome.

Conflict of interest: None.

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GASTRO-INTESTINAL *MYCOBACTERIUM AVIUM* COMPLEX AS A CAUSE OF ANAEMIA

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Anaemia is a relatively common finding in HIV-positive patients, with rates (among females) as high as 37%, compared with their HIV-negative counterparts (17%). Anaemia of chronic disease plays a very important role in this population group, and is estimated to occur in 18 - 95% of cases. For this reason, it is imperative to distinguish this condition from other underlying or concurrent causes of anaemia that may warrant treatment. This clinical case illustrates the value of critically evaluating the parameters of a full blood count and haematinic screen, to so determine which patients warrant further workup.

CASE REPORT

A 43-year-old man, known to be HIV-1 positive, presented to the casualty department at Kalafong complaining of a 2-week history of fatigue, weight loss, night sweats, dysphagia and general malaise. He further described a 3-day history of vomiting and diarrhoea, with no melaena or haematemesis.

At the time of presentation, he had been on first-line highly active antiretroviral (HAART) therapy for 2 years. Despite this the CD4 count on admission was 3 cells/µl. In the light of this finding, non-compliance was suspected. He had previously been diagnosed with

disseminated *Mycobacterium avium-intracellulare* by positive blood cultures and had been started on treatment. Owing to side-effects, he had not complied with this treatment regimen either.

On admission he was pyrexial and tachycardic. He was clinically anaemic with no signs of oral hairy leukoplakia or candida. Although abdominal examination was unremarkable (with no hepatomegaly or splenomegaly), he was tender in the epigastric area. Cardiovascular and respiratory examinations were essentially normal.

The full blood count revealed a significant microcytic hypochromic anaemia (haemoglobin 5.8 g/dl, mean corpuscular volume 68 fl and mean corpuscular haemoglobin 20.4 pg). The white cell count was normal, but he had thrombocytopenia (30×10^9/l). Creatinine and electrolyte levels were normal. Liver function tests revealed an isolated mildly raised gamma-glutamyl transpeptidase (GGT) level (70 U/l) and a low albumin level (16 g/l). C-reactive protein was elevated at 84.9 mg/l. Iron studies were also performed and showed low serum iron (1.3 µmol/l) and transferrin (1.4 g/l) levels and transferrin saturation (4%), and a markedly elevated serum ferritin level (1 579 µg/l).

As part of the work-up for anaemia, the upper gastro-intestinal tract was investigated by endoscopy. This revealed what was clinically judged to be extensive candidiasis throughout the oesophagus. The stomach was normal but the duodenum also had extensively distributed white plaques. A biopsy specimen of these plaques was taken and submitted for histological examination. An H&E stain was performed (Fig. 1, a). The periodic acid-Schiff (PAS) stain revealed multiple clusters of micro-organisms in the histiocytes (Fig. 1, b). Finally, a Ziehl-Neelsen (ZN) stain was performed, showing large numbers of acid-fast bacilli (Fig. 1, c and d). A diagnosis of disseminated *M. avium* complex (MAC) was suggested, as the organisms were found intracellularly. The diagnosis of disseminated MAC was confirmed on a urine sample by molecular techniques.

DISCUSSION

Patients with advanced HIV-1 disease pose a multitude of challenges in terms of diagnosis and treatment. Anaemia is a relatively common finding in HIV-positive patients, with rates (among females) as high as 37%, compared with their HIV-negative counterparts (17%).[1] The list of possible causes of anaemia in HIV-positive patients is substantial and differentiation is often difficult. Value is certainly added by taking the full blood count results into consideration. A simple distinction between red cell size (reflected in mean corpuscular volume) and red cell haemoglobin content (reflected by mean corpuscular haemoglobin) can significantly contribute to further choices in testing.

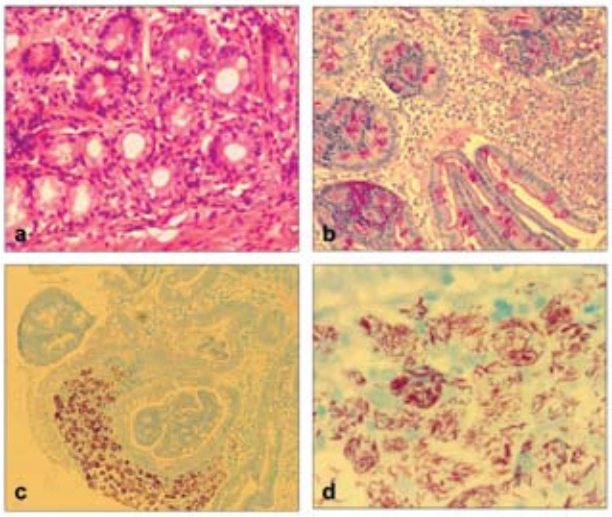

Fig. 1. Sections from white plaques biopsied in duodenum: a – H&E stain; b – PAS stain showing numerous clumps of organisms in histiocytes; c – ZN stain showing clumps of acid-fast bacilli; d – closer view of collection of acid-fast bacilli in ZN stain.

Anaemia of chronic disease plays a very important role in this population group, as inhibition of iron transfer from the reticulo-endothelial cells to the erythroid precursors due to inflammation is estimated to occur in 18 - 95% of cases.[2] For this reason, it is imperative to distinguish this condition from other underlying or concurrent causes of anaemia that may warrant treatment. A haemoglobin level below 8 g/dl should prompt further investigation, as anaemia of chronic disease rarely causes World Health Organization grade III or IV anaemia[2] (grade III <7.9 g/dl, grade IV <6.5 g/dl).[1] Iron studies may facilitate this process. In both iron deficiency anaemia and anaemia of chronic disease, the serum iron level and transferrin saturation will be reduced. The transferrin level, however, may facilitate in making a distinction as it is typically reduced to normal in anaemia of chronic disease and increased in iron deficiency. A further indicator can be found in serum ferritin levels, which are reduced to below 30 ng/l (positive predictive value of 92 - 98%) in iron deficiency, and normal to elevated in anaemia of chronic disease. The inherent confounder with using ferritin is the fact that it acts as an acute-phase reactant and will be elevated beyond its baseline in any inflammatory condition, irrespective of iron status.[2]

The soluble transferrin receptor level may be a useful assay to delineate causes of anaemia. Levels are typically increased in iron deficiency and essentially normal in anaemia of chronic disease, as inflammatory cytokines negatively influence its expression. This can also be very useful if co-existence of both conditions is suspected. However, the assay is not universally offered. The use of various ratios has also been proposed as possibly helpful in determining the underlying cause of anaemia.[2]

The finding and confirmation of iron deficiency should prompt further investigation as to the underlying cause.

Imaging of the gastro-intestinal tract may be useful, especially if clinical features are suggestive. Of note is the fact that the only feature suggestive of upper gastro-intestinal bleeding in our patient was the epigastric tenderness on abdominal examination. It is therefore prudent to have a high index of suspicion. Again, the differential diagnosis in this clinical setting is large and relates to the degree of immunosuppression.[3]

Disseminated MAC is the most common bacterial opportunistic infection among HIV-1-positive patients in the First World.[4] However, it appears to be less common in our local setting.[5] It has been postulated that it is caused by the overwhelming presence of *M. tuberculosis* in the South African context.[5] Patients with a CD4 count below 50 cells/µl and possibly high HIV-1 viral loads are at increased risk of MAC infections, which have been shown to be an independent predictor of mortality. For this reason prophylaxis is advocated by some.[4] It is, however, not included in the current South African *National Antiretroviral Treatment Guidelines.*[6]

MAC can affect any part of the gastro-intestinal tract, with the duodenum being the most common site. Macroscopic findings are not diagnostic. Biopsy and culture is therefore the mainstay of diagnosis of this condition.[3]

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Invited Comment

Abdominal mycobacterial infection in HIV

The articles in this edition by Kao and Hung and Van de Vyver and Visser both deal with aspects of abdominal mycobacterial infections. Van de Vyver's article highlights the importance of investigating abnormalities that cannot be attributed to HIV infection alone, and demonstrates that abdominal mycobacterial infection may present with a paucity of abdominal symptoms and signs. While tuberculosis (TB) infection is predominant in South Africa, non-tuberculous mycobacteria should always be considered in patients with advanced immunosuppression. The article by Kao demonstrates a more dramatic presentation in a patient with relatively preserved immunity. Notification rates of extrapulmonary TB in South Africa are increasing, and it is likely that more patients will present with abdominal tuberculosis.[1] Tuberculosis can involve the entire gastro-intestinal tract, from the intra-abdominal organs to the peritoneum. The spectrum of symptoms seen in abdominal TB range from insidious nonspecific complaints that may be mistaken for the constitutional symptoms of HIV infection, to an acute abdomen.[2] With improved access to antiretrovirals, TB immune reconstitution inflammatory syndrome is being seen more frequently and often involves the abdomen.[3]

In resource-limited facilities, investigations such as abdominal computed tomography scanning and laparoscopic peritoneal biopsy are seldom available. However, abdominal ultrasound, specifically looking for hepatomegaly, ascites, splenic micro-abscesses and intra-abdominal lymphadenopathy, is a useful investigation for assessing HIV-infected patients with suspected abdominal tuberculosis.[4]

Clinicians need to maintain a high index of suspicion for TB in patients with HIV and abdominal symptoms. In the correct clinical setting empiric anti-tuberculosis therapy is warranted. All patients started on anti-tuberculosis therapy need close follow-up until resolution, and those who fail to respond to TB therapy may require further investigation. Non-tuberculosis mycobacterial infection should be considered in patients with advanced immune deficiency.

While abdominal tuberculosis in HIV-infected patients is best managed with standard TB therapy and anti-retrovirals, complications such as obstruction, perforation and large abscess formation may require surgical intervention.[2] Depending on clinical presentation, early consultation with the surgeons is essential and if required surgery should not be delayed.

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REVIEW

EFAVIRENZ IN PREGNANCY

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Clinical guidelines from the National Department of Health (DoH), South Africa, for prevention of mother-to-child transmission (PMTCT), revised in 2010, recommend that HIV-positive pregnant women with a CD4 count of 350 cells/µl or less commence lifelong antiretroviral therapy (ART).[1]

DoH guidance for women initiating ART in pregnancy in the public sector – on which the overwhelming majority of HIV-positive South Africans rely for their care – recommends they receive nevirapine with tenofovir and lamivudine or emtricitabine at any stage of gestation. In cases where a woman is already receiving ART with an efavirenz-based regimen, it is recommended that this should be substituted for nevirapine if she is still in the first trimester of pregnancy. Efavirenz is therefore contraindicated in pregnant women at any time during pregnancy; for those already receiving the drug, it is only switched in the first trimester.

The concern about the use of efavirenz in pregnancy dates back to preclinical studies. It is the only antiretroviral with preclinical primate data and in turn has the strongest US Food and Drug Administration (FDA) category and the most scrutiny during pregnancy.[2] The drug also has the most conflicting recommendations, both from guidelines and product labelling.

This article is a summary of what we know (and do not know) about using efavirenz in pregnancy. We argue that reconsideration of the risk and benefits of this evidence, which has informed South African guidance, is warranted.

MIXED MESSAGES FROM PRECLINICAL DATA, GUIDELINES AND LABELLING

During the development of efavirenz, animal studies were conducted to assess its potential for birth defects. These primate data are likely to have made providers and regulators more aware of the potential risks with efavirenz.

Malformations were observed in three out of 20 monkey offspring from efavirenz-treated cynomolgus monkeys (versus none among 20 controls) in a developmental toxicity study. The monkeys were dosed throughout pregnancy with a dose resulting in plasma drug concentrations similar to those in humans given 600 mg/day of efavirenz. Anencephaly and unilateral anophthalmia were observed in one monkey infant, micro-ophthalmia was observed in another, and cleft palate was seen in a third. As a consequence of this trial, efavirenz was classified as FDA category C.

In 2005, efavirenz was reclassified as FDA category D, indicating an established risk to the human fetus. This classification was based on three reports of myelomeningocele and one of Dandy-Walker syndrome to the Antiretroviral Pregnancy Register (APR).[3] Each defect was reported retrospectively and therefore the relative risk cannot be calculated, as the denominator is unknown. Two of the reported cases of myelomeningocele (spina bifida) and the case of Dandy-Walker syndrome were reported in aborted fetuses.

The low quality of evidence regarding the safety of efavirenz in pregnancy has led to much uncertainty

when making recommendations. This is particularly problematic for guidance in low- and middle-income countries such as South Africa, with few antiretroviral options and a public health approach. However, the APR provides some reassurance, as does a meta-analysis performed earlier this year.[4]

Both the registry and the meta-analysis suggest that a twofold increase in overall birth defects can be excluded, but some caution about the potential for increased neural tube defects remains because of the primate data. This, however, needs to be taken in the context of a low incidence of neural tube defects in the general population, which varies from country to country, and is in the range of 0.1% (South Africa is 0.36%). With current data it is only possible to exclude a potential tenfold or higher increase in risk, but as the authors of the meta-analysis described below suggest, even a fivefold increase would give an overall increase of less than 1%. It is also important to take into consideration that the neural tube closes by approximately 28 days' gestation, so the potential risk is for women receiving the drug in the first trimester. Since pregnancies are seldom recognised by this stage, if there is a risk it would be in women who conceive while already taking efavirenz.

This uncertainty has led to differences in interpretation when making recommendations. The World Health Organization (WHO) pregnancy guidelines recommend that efavirenz should not be initiated in the first trimester, but may be initiated in the second and third trimesters.[5] The WHO adult guideline panel was unable to conclude from the evidence available whether there were benefits associated with the use of efavirenz compared with nevirapine in pregnant women after the first trimester and with higher or unknown CD4 cell counts. However, they note that more than half the panel members preferred efavirenz in these situations.[6]

US guidelines also state that efavirenz use can be considered after the first trimester. Other countries such as Zambia concur, although most European guidance is similar to South Africa.[7-9]

The British HIV Association (BHIVA) recommends: 'Until more robust data are available it remains advisable to avoid efavirenz for women who may conceive.'[10] These guidelines highlight two issues to consider for women who do conceive on efavirenz: the gestational age at presentation and the plasma half-life of efavirenz. They explain that, after stopping, it can take up to 3 weeks for efavirenz to clear from the plasma. Whether there is a key period during the first 6 weeks of fetal development when efavirenz affects central nervous system (CNS) development is unknown, as is the minimal teratogenic dose. They suggest 'discontinuing efavirenz after neural tube closure will not influence the outcome'.

Furthermore, the prescribing information accompanying the drug is inconsistent. Bristol-Meyers Squibb (BMS) markets the originator efavirenz product (sold as Sustiva in the USA, Canada and some countries in the European Union). Their package insert states: 'Fetal harm can occur when administered to a pregnant woman during the first trimester.'[11]

Merck Sharp and Dohme (MSD, who market efavirenz as Stocrin in South Africa and many other parts of the world) provides prescriber information for efavirenz that cautions against conception in patients already on efavirenz as opposed to the prescription of efavirenz in women already known to be pregnant, in line with the WHO and BHIVA recommendations focusing on very early gestational risk. Their package insert states that 'pregnancy should be avoided in women receiving Stocrin®'.[12]

The generic manufacturer Aspen states: 'The use of Aspen efavirenz during pregnancy is not recommended, as teratogenicity has been noted.'[13]

THE ANTIRETROVIRAL PREGNANCY REGISTRY

The APR is an international registry started in 1989 to prospectively monitor potential birth defects in infants exposed to antiretrovirals *in utero*. It is one of the largest ongoing pregnancy registries in the world.

The objectives of the registry are to provide early warning of major teratogenicity, estimate the risk of birth defects, and collect supplementary data from animal, clinical and epidemiological studies. Data collection is through voluntary enrolment by those providing health care to pregnant women exposed to antiretrovirals, and in turn infant follow-up. The registry has summaries of relevant data for all registered antiretrovirals, and reports are updated twice a year.

The majority of reports (84.9%) are from the USA, with small numbers from elsewhere (e.g. 1.9% from South Africa). One of the current goals of the registry is to increase non-US reporting.

As of the last review, through January 2010, the prevalence of birth defects per 100 live births among women with first-trimester exposure to any antiretroviral was 2.8% (95% confidence interval (CI) 2.3 - 3.3). At this review there were 13 575 pregnancies enrolled in the registry, of which 11 867 (87.4%) reports, of which 5 582 were first-trimester exposures, were used in the analysis. The overall rate reported is not significantly different from the prevalence of defects among women with initial exposure during the second and/or third trimester (2.5 per 100 live births).

Only 14 defects have been recorded in 546 infants born following first-trimester efavirenz exposure (2.6%, 95% CI 1.4 - 4.3%). These include a single case of myelomeningocele and a single case of anophthalmia with severe oblique facial clefts and amniotic banding.

It is worth noting that since the incidence of myelomeningocele in the USA is 4.3 per 10 000 live births it would be expected that the number of cases observed in the prospectively reported register should be greater than this overall.

META-ANALYSIS

Earlier this year, Ford *et al.* performed a systematic review of databases (to 2 February 2010) in order to identify observational cohorts reporting birth outcomes among infants exposed to maternal efavirenz during the first trimester of pregnancy. The findings from this analysis were published in *AIDS* in June 2010. Slightly modified data (to take in the updated APR report in January) were presented at IAS 2010.[14] Besides birth defects of any kind the investigators looked at spontaneous abortions, termination of pregnancy, stillbirths and preterm delivery.

The investigators found that 16 studies met the inclusion criteria for the analysis. These included 11 prospective and 5 retrospective cohorts. Nine studies were conducted in low and middle-income countries. Six were European and one primarily in the USA. Eight were reported in journal articles, and 6 as conference abstracts, one (MTCT-Plus) was an unpublished cohort and one the APR report.

This analysis found a pooled non-significant relative risk for efavirenz versus non-efavirenz of 0.85 (95% CI 0.60 - 1.21%, p=0.47). The investigators found low heterogeneity between studies (I^2 = 0, 95% CI 0 - 56.3%, p=0.85). The overall prevalence of birth defects was 2.9% (95% CI 2.1 - 4.0%), range 0 - 22.6% (95% CI 9.6 - 41%). This is similar to the ranges observed in the general population: 2.7%, 2.5% and 2.5 - 8% in the USA, France and South Africa, respectively.

There was 1 infant out of 1 301 with a neural tube defect (myelomeningocele), giving a prevalence of 0.08% (95% CI 0.02 - 0.43%). This is also similar to the ranges in the general population, but, as the investigators noted, the upper CI would give a higher prevalence, including than that of South Africa. The relative risk between those exposed in the first trimester versus second/third trimester did not differ (RR=0.91, 95% CI 0.46 - 1.79%, p=0.79).

Stillbirth, spontaneous abortion and preterm delivery were also within the range of the general population.

Rates of termination of pregnancy ranged from 5.3% (95% CI 0.64 - 17.7%) to 33.7% (95% CI 23.7 - 44.9%). The investigators noted that one study in Soweto found a relative risk of termination 5.73 times higher (95% CI 1.45 - 22.75%, p=0.0017) among women receiving efavirenz compared with other antiretroviral drugs, highlighting a need for careful counselling of women and attitudes among providers.

DATA FROM FRERE HOSPITAL

After the APR, the second largest data set included in the meta-analysis was from a large regional cohort in South Africa.[15] This is also the largest study to date of efavirenz-based ART exposure from the second trimester onwards.

In this study Bera *et al.* evaluated data from the Efavirenz in Pregnancy Registry, which is prospective and based at the Frere Hospital in East London (a referral hospital for a large area of the Eastern Cape) and set up in January 2006. Women who conceived on efavirenz and presented in the first trimester were offered the choice of termination of pregnancy (to 20 weeks' gestation) or switched to another drug. Women who presented at 14 weeks or later and were eligible for ART were initiated on an efavirenz-based regimen. Between 1 January 2006 and 31 December 2008, 744 women were initiated on efavirenz-based regimens from the second trimester onward. Of these, 89 women were still pregnant at the time of evaluation and 32 were lost to follow up.

During the same period, 220 women conceived while receiving efavirenz-based ART and 42 while receiving nevirapine-based ART. Of this group, 17 and 7 women were still pregnant and 8 and 2 women were lost to follow-up receiving efavirenz and nevirapine, respectively.

Women who had received efavirenz-based ART throughout the entire first trimester were classified as 'complete first-trimester exposure' and those who substituted efavirenz for another drug as 'partial first-trimester exposure'.

This analysis evaluated data from 851 women with pregnancy outcomes.

Of 623 women initiated on efavirenz in pregnancy, birth defects occurred in 16 live births, a prevalence of 2.6% (95% CI 1.5 - 4.2). In 195 women who conceived while receiving efavirenz, birth defects occurred in 5/184 live births and 1/4 stillbirths, a prevalence of 3.3% (95% CI 1.2 - 7.0). In this group, 93% received efavirenz-based ART for longer than 1 month before conception and all pregnancies were unintended.

There were no significant differences in the prevalence of birth defects between the first- and second/third-trimester exposure (prevalence ratio 1.27, 95% CI 0.5 - 3.20, p=0.301). Neither were there differences between complete (4/131; 3.1%) and partial (2/53; 3.8%) efavirenz exposure (prevalence ratio 0.81, 95% CI 0.15 - 4.29, p=0.556).

Worth noting is that there was also a birth defect in 1 out of 33 live nevirapine-exposed infants, a prevalence of 3.0% (95% CI 0.1 - 15.8). The prevalence ratio of birth defects following conception on efavirenz compared with nevirapine was 1.08 (95% CI 0.13 - 8.65, p=0.69). However, the numbers of nevirapine exposures are far too small to draw any conclusions.

CONFLICTING FINDINGS IN RETROSPECTIVE STUDY PACTG 219/219C

Finally, a study of children enrolled in PACTG protocols 219 and 219C – a multisite US cohort of children born to HIV-positive women set up to study the long term effects of *in utero* antiretroviral exposure – recently reported a higher prevalence of birth defects than found in other paediatric cohorts.[16]

This observation was difficult to interpret as exposed children were enrolled retrospectively up to 1 year of age (only prospective pregnancies are enrolled in the APR), and for reasons discussed below.

Protocol 219 followed HIV-infected and uninfected children from May 1993 to August 2000. Children were eligible if their mothers were enrolled in a PACTG trial in pregnancy. In September 2000, protocol 219C was introduced, amending 219 to remove the eligibility criterion mandating enrolment in another PACTG trial. Birth defect data were recorded at study visits. Protocol 219 did not include a direct question about birth defects; 219C included this question.

The primary determinant was first-trimester exposure. Overall antiretroviral exposure, classes of antiretrovirals and specific antiretrovirals to which at least one child with a birth defect had first-trimester exposure were evaluated.

The reference group was children unexposed to the particular antiretroviral (or class of drug) during the first trimester, which included antiretroviral-unexposed children, those only exposed in labour, those unexposed to the particular drug but exposed to other antiretrovirals, and children only exposed beyond the first trimester.

Clinicians were blinded to antiretroviral exposure and the outcome was presence of a birth defect within the first year of life.

A total of 117 children with at least one defect were reported out of the study population of 2 202 children. This gave an overall defect prevalence of 5.3% (95% CI 4.4 - 6.3) and 4.7% (95% CI 3.8 - 5.6) if just the 103 cases of major defects were included. The prevalence was 4.8% (95% CI 3.7 - 6.1) in children unexposed in the first trimester and 5.8% (95% CI 4.2 - 7.8) in exposed children. The majority of defects occurred in the heart and musculoskeletal system. A higher defect rate (5/32, 15.6%) was reported among children exposed to efavirenz in the first trimester compared with unexposed children, adjusted odds ratio 4.31 (95% CI, 1.56 - 11.86). The defects included 1 laryngomalacia, 1 meningomyelocele, 1 hypospadias, 1 club foot, 1 hypertonicity of extremities and 1 cleft palate.

There was also an association in children exposed to lopinavir/ritonavir, but when adjusted for first-trimester folate antagonist exposure, year of birth and perinatal study participation this did not persist (p=0.07), whereas the association with efavirenz continued.

It is difficult to know whether this study advances or confuses the field. Although based on 2 202 children, only a third (763) were exposed to any antiretroviral during the first trimester, compared with over 5 000 in the APR. Consequently, with the exceptions of zidovudine, lamivudine and nelfinavir, few children were exposed to individual drugs, which accounts for the wide range of odds ratios and CIs. A similar phenomenon has been observed over the years in the APR with new antiretrovirals, which is followed by a gradual movement towards the mean as the denominator increases, suggesting that initial case notification may drive initial reports to the registry.

The findings also generally differ from the APR, in which only didanosine (4.5%, 95% CI 2.6 - 7.1%) has attracted attention owing to a small but persistent increase in risk of birth defects, while PIs in general, and lopinavir/ritonavir (1.7%, 95% CI 0.8 - 3.1%) in particular, have generally been found to be associated with no increase in risk.

As might be anticipated, folate antagonist exposure during the first trimester was associated with an increased prevalence of birth defects, although data were largely incomplete and the observation did not reach statistical significance. The observed confounding of this risk with lopinavir/ritonavir exposure is a reminder not to forget the obvious.

DISCUSSION

There is to date no evidence of an increase in the incidence of birth defects among infants exposed to efavirenz beyond the first trimester, and excluding the retrospective analysis, also no increase among infants

born to women receiving efavirenz in the first trimester. However, the authors of the meta-analysis note several limitations to the evidence base, including few studies reporting risk of bias or attempting to control for potential confounders, and most importantly the limited sample size.

They suggest that although these data should provide reassurance to providers regarding first-trimester exposure, the low incidence of neural tube defects in the general population means a larger sample size is still needed to rule out the increased risk of this specific defect.

They write: 'The balance of risks and benefits of efavirenz in pregnancy merits some recalibration, particularly in resource-limited settings where drug formularies are limited, women of child bearing age represent the majority of those infected with HIV, coinfection with tuberculosis is frequent, and the risk of mortality for those who are eligible for ART is high.'

The approach in the new South African guidelines to use of efavirenz is far more cautious than that of the WHO. Whereas the WHO interpreted the risk as being limited to the first trimester, and allowed for the possibility that some risk may still exist only from first-trimester exposure in spite of the low-quality, conflicting evidence, the South African guidelines do not recommend its inclusion at all in pregnancy.

The South African guidelines rely on the 2004 approved package insert for Stocrin, which the Medicines Control Council (MCC) believes indicates an absolute bar on the use of efavirenz throughout pregnancy. However the MCC is open to revisiting this package insert should the applicant – in this case MSD – apply for an amendment and supply sufficient scientific data to justify the amendment.

Although it may be prudent to guide prescribers to avoid first-trimester exposure, there seems to be strong rationale to recommend the use of efavirenz in pregnancy in South Africa beyond this period, for the following reasons:

Simplification to maximise adherence. Efavirenz must be taken once a day whereas nevirapine is usually dosed twice a day with a 2-week induction phase. The other components of ART are dosed daily; use of nevirapine over efavirenz converts a once-daily to a twice-daily regimen.

Consistency with adult treatment regimens. Efavirenz plus tenofovir plus lamivudine or emtricitabine is recommended for almost all non-pregnant adults.

Simplicity of monitoring. Efavirenz does not usually require additional blood tests to the overall regimen. Nevirapine requires baseline alanine aminotransferase (ALT), and liver function tests (LFT) if the baseline ALT is abnormal or if patients develop a rash, any significant mucocutaneous reactions, fever, jaundice or abdominal pain.

Reduction in incidence of toxicity:

- Efavirenz compared with nevirapine is a safer drug with respect to adverse events, particularly for severe adverse events.
- In a representative South African adult population, 7.6% of patients who started ART with nevirapine had to stop the drug due to toxicity by 3 years, compared with 1.9% of those starting ART with efavirenz having to stop efavirenz due to toxicity. Most of the nevirapine substitutions were in the first 3 months of treatment.[17]
- Nevirapine has been associated with an increased risk of toxicity in women with a CD4 count greater than 250 cells/µl in early studies, and a box warning to this effect has been included. The WHO reviewed the literature and felt reassured to initiate nevirapine in women with high CD4 cell counts. Subsequent to this review an article representing over 10 000 patients treated with nevirapine-based ART suggested a high CD4 cell count in treatment-naïve patients to be a risk factor for nevirapine toxicity.[18,19]

Co-tuberculosis (TB) treatment:

- Efavirenz has better blood levels when used with anti-TB treatment, specifically rifampicin, compared with nevirapine, resulting in slightly lower treatment failure.[20]
- The first-line ART choice in the current South African guidelines for a patient with TB would be tenofovir *plus lamivudine* or emtricitabine plus efavirenz in all patients whether pregnant or not, at odds with the rationale for not recommending efavirenz in pregnant women who do not have tuberculosis.
- Rash that occurs during co-administration may be due to the TB drugs or nevirapine, and it may occasionally be difficult to determine which to stop.

Availability of fixed-dose combinations (FDCs):

- Efavirenz is included in a couple of FDCs that are pending registration in South Africa – these are tenofovir plus lamivudine plus efavirenz, and tenofovir plus emtricitabine plus efavirenz. The FDA has already tentatively approved such products (tentative only in that patent protection currently prevents them from being marketed in the USA).
- FDCs facilitate adherence and simplify the taking of treatment. They take up less space, with transport and storage savings.

It is instructive that in the USA, in 2009, among pregnant women receiving NNRTI-based ART, over four times as many receive efavirenz compared with nevirapine.[21] In a UK cohort, nearly 20% of women receiving an NNRTI regimen before conception received efavirenz.[22]

Bera *et al.* above[15] note that all the pregnancies in the women conceiving on efavirenz in their cohort were unintended, and an investigation into the correct application of guidelines in Johannesburg revealed that the majority (77 - 90%) of women were incorrectly assigned to efavirenz with respect to contraception use, and 39% were either trying to conceive or planned to do so in the next year.[23]

CONCLUSION

In short, the recommendation for nevirapine in pregnancy, based on poor data concerning the first trimester and without rationale beyond the first trimester, will result in women being exposed to a more toxic and more complicated regimen, which has significant additional operational challenges and differs from the otherwise very uniform approach to first-line ART provision to adults in the national programme. If indeed there is a concern about neural tube defects, the appropriate guideline response should be to focus on the avoidance of conception in women on efavirenz in line with the WHO recommendations and the prescriber information that accompanies efavirenz when distributed as Stocrin.

This real risk to maternal health and in turn child health must be weighed up against the theoretical risk of fetal toxicity. We believe that the decision to uniformly use nevirapine in pregnancy is a poor one in the absence of better data, and should be reviewed by the MCC and the Department of Health.

Thanks to Graham Taylor and Karen Beckerman.

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ORIGINAL ARTICLE

IMMUNE RECONSITUTION INFLAMMATORY SYNDROME AMONG ADOLESCENTS: A REPORT OF CASES IN A RESOURCE-LIMITED SETTING (UGANDA)

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We report immune reconstitution inflammatory syndromes in a cohort of adolescents/young adults over a period of 1 year at the Infectious Diseases Institute, Kampala, Uganda.

The immune reconstitution inflammatory syndrome (IRIS) is a frequent early complication of antiretroviral therapy (ART), particularly in patients who commence ART with low CD4 counts and established opportunistic infections. IRIS in HIV-infected patients results from a pathological inflammatory response to pre-existing infective, host or other antigens, alive or dead, causing clinical deterioration after initiating ART.[1] The most common forms of IRIS occur in association with mycobacterial and herpesvirus infections.[2]

Adolescents and young adults comprise an increasing proportion of new HIV infections both in developing and developed countries, and little is known regarding HIV IRIS in this group. As the ART roll-out has gathered pace since 2004 in resource-limited settings, adolescent IRIS has emerged as a clinical challenge. We describe adolescent/young adult patients who presented to our clinic with IRIS events.

METHODS

The study was performed at the Adult Infectious Diseases Institute (IDI) at Mulago Hospital, Kampala, Uganda. The AIDC is part of the Makerere University Infectious Diseases Institute and provides HIV care, including free ART, to HIV-infected patients with a CD4+ count <200 cells/µl or with World Health Organization stage IV disease. The study was approved by the ethics panel and the Institutional Review Board since this was a case series. Among our adolescent/young adult cohort aged 16 - 24 years of about 480, we have seen 6 cases of IRIS, including cryptococcal meningitis IRIS, Kaposi's sarcoma IRIS, herpes zoster IRIS, pulmonary tuberculosis IRIS and 2 cases of oral candidiasis IRIS within the past 12 months. The incidence of IRIS after initiation of HAART was 1.25%. The median age of presentation was 22 years and the median CD4+ count before commencing ART 65 cells/µl. IRIS presented a median of 6 weeks from the start of HAART (range 3 - 16 weeks).

Mycobacteria are by far the most common pathogens associated with IRIS in HIV-infected patients.[3-7] Other infections that have been associated with IRIS events include varicella zoster, herpes simplex, meningeal cryptococcosis, hepatitis, cytomegalovirus retinitis, progressive multifocal leuco-encephalopathy and intestinal parasites. While the majority of IRIS events are infectious in nature, auto-immune IRIS reactions have also been described in adults.[8]

DISCUSSION

IRIS is a condition seen in some cases of AIDS or immunosuppression, in which the immune system begins to recover but then responds to a previously acquired opportunistic infection with an overwhelming inflammatory response that paradoxically makes the symptoms of infection worse.[9] It is thought that the immunopathological response initiated by HAART restores the immune response against pathogenic antigens.[10] There is paradoxical worsening of pre-existing infectious processes following initiation of HAART in HIV-infected individuals.[9]

These cases highlight the risks faced during immune reconstitution in adolescent and young adult patients who commence ART with advanced immunosuppression.

TABLE I. TABLE DISPLAYING AGES, ABSOLUTE CD4 COUNTS AND PRESENTATION TIME OF IRIS AMONG ADOLESCENTS/YOUNG ADULTS OVER 1 YEAR AT THE INFECTIOUS DISEASES INSTITUTE, KAMPALA

Age (yrs)	CD4 counts at initiation of HAART (cells/µl)	IRIS condition	Time from start of HAART to onset of IRIS (wks)
19	45	Pulmonary tuberculosis	4
20	77	Oral candidiasis	6
21	56	Kaposi's sarcoma	3
23	65	Herpes zoster	9
24	65	Cryptococcal meningitis	16
24	73	Oral candidiasis	6

CONCLUSION

IRIS occurs in adolescents and young adults, but little is known about IRIS in general and minimal research has been conducted in the adolescent/young adult age group.

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LETTER • LETTER • LETTER • LETTER

SANBS'S POLICY ON BLOOD DONATIONS FROM MEN WHO HAVE SEX WITH MEN

To the Editor: We at the South African National Blood Service (SANBS) are acutely aware of the issues surrounding the exclusion of men who have sex with men (MSM) from donating blood and the negative emotions that surround this policy. I would like to assure readers that SANBS does not make such decisions lightly, and we constantly review policies based on the latest scientific findings. It is perhaps time to review the basis of the current policy and engage in debate on its scientific merit.

It is, however, important to clarify a few misconceptions regarding our policies on the sexual activities of our donors.

In an editorial comment on 6 January 2010, the editor of *The Herald* newspaper in Port Elizabeth stated: 'A pattern of multiple partners or of unprotected sex ... is clearly also high-risk and yet heterosexual donors who may be sexually reckless are spared prying questions and the possible refusal of their offer of blood.'[1] This statement is factually incorrect. When donating blood, *all* donors, whatever their sexual orientation, have to answer very personal questions regarding their sexual activities during the preceding 6 months.[2]

Any person who has had any form of potentially high-risk sexual activity will be deferred for a period of 6 months following the high-risk activity. A donor who has multiple sex partners will be regarded as being at potentially high risk regardless of sexual orientation. At no point does SANBS suggest that high-risk sexual practices are exclusive to the gay community, hence the self-exclusion questionnaire's comprehensive set of questions regarding various sexual activities and practices.

There are over 450 rules guiding donor selection with

regard to medical conditions and lifestyle, and there are many groups of people whom we defer from donating, either temporarily or permanently.[3] Some individuals in these groups may have a very low risk of blood-borne infections and their blood would probably be safe to give to patients, but since it is impossible to identify specific individuals at low risk it is safest to ask everyone in the higher risk groups not to donate blood.

The request not to donate blood can be disappointing and frustrating to some people who wish to do so. Our decisions are based on information and research about the effects our policies on blood supply safety, not out of a desire to discriminate against any particular group.

The aims of donor selection are to:

- select donors whose blood is most unlikely to transmit any infection
- collect enough blood to meet patients' needs
- make sure that donors themselves come to no harm through the blood donation process.

We have to balance these three aims while keeping the selection process clear and simple, bearing in mind that almost a million units of blood are collected each year – a mammoth task complicated by stringent quality control and logistics.

The preliminary findings of recent studies among MSM, such as the JEMS study conducted in Johannesburg and Durban and the Soweto Men's Study, have found their HIV prevalence to be more than double the Actuarial Scientists of South Africa (ASSA)'s estimate of a 15.5% national HIV prevalence and the UNAIDS estimate of 18.1%.[4-8]

South Africa was one of the first countries in the world to lift the total ban on men who have sex with men donating blood. Other countries such as Sweden are only now starting to follow our example. We still have among the most progressive policies regarding MSM in the world, and while this may not be much consolation to gay men in stable relationships, it is testimony to SANBS's commitment to be as inclusive as possible with regard to the community we serve.

Internationally this is a very topical discussion. It is interesting to note that in the USA some politicians have called for the lifting of the ban against MSM donating blood and that this was countered by the Haemophiliac Society, a group whose members were severely affected by infected blood during the 1980s.

It is easy to get lost in all the numbers and emotions, but at SANBS we have the very tough responsibility of weighing up the right of an individual to donate blood against that of a patient to receive blood that is as safe as it is humanly possible to make it. The decision on which groups of the population will be or should be allowed to donate must be taken on the basis of scientific merit and the blood service's ability to implement policies that are clear and concise.

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ERRATUM

In 'Changes to the ART guidelines – an overview', which appeared on pp. 28 - 30 of the April 2010 issue of the *Journal,* the first sentence under the heading 'National regimens' and the heading to Table I should have read 'National regimens for adults and adolescents' and not 'National regimens for children and adolescents'. We apologise for these errors and have corrected them on the web version of the article, in which there are also other adjustments.

ORIGINAL ARTICLE

IMMUNE RECONSITUTION INFLAMMATORY SYNDROME AMONG ADOLESCENTS: A REPORT OF CASES IN A RESOURCE-LIMITED SETTING (UGANDA)

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We report immune reconstitution inflammatory syndromes in a cohort of adolescents/young adults over a period of 1 year at the Infectious Diseases Institute, Kampala, Uganda.

The immune reconstitution inflammatory syndrome (IRIS) is a frequent early complication of antiretroviral therapy (ART), particularly in patients who commence ART with low CD4 counts and established opportunistic infections. IRIS in HIV-infected patients results from a pathological inflammatory response to pre-existing infective, host or other antigens, alive or dead, causing clinical deterioration after initiating ART.[1] The most common forms of IRIS occur in association with mycobacterial and herpesvirus infections.[2]

Adolescents and young adults comprise an increasing proportion of new HIV infections both in developing and developed countries, and little is known regarding HIV IRIS in this group. As the ART roll-out has gathered pace since 2004 in resource-limited settings, adolescent IRIS has emerged as a clinical challenge. We describe adolescent/young adult patients who presented to our clinic with IRIS events.

METHODS

The study was performed at the Adult Infectious Diseases Institute (IDI) at Mulago Hospital, Kampala, Uganda. The AIDC is part of the Makerere University Infectious Diseases Institute and provides HIV care, including free ART, to HIV-infected patients with a CD4+ count <200 cells/µl or with World Health Organization stage IV disease. The study was approved by the ethics panel and the Institutional Review Board since this was a case series. Among our adolescent/young adult cohort aged 16 - 24 years of about 480, we have seen 6 cases of IRIS, including cryptococcal meningitis IRIS, Kaposi's sarcoma IRIS, herpes zoster IRIS, pulmonary tuberculosis IRIS and 2 cases of oral candidiasis IRIS within the past 12 months. The incidence of IRIS after initiation of HAART was 1.25%. The median age of presentation was 22 years and the median CD4+ count before commencing ART 65 cells/µl. IRIS presented a median of 6 weeks from the start of HAART (range 3 - 16 weeks).

Mycobacteria are by far the most common pathogens associated with IRIS in HIV-infected patients.[3-7] Other infections that have been associated with IRIS events include varicella zoster, herpes simplex, meningeal cryptococcosis, hepatitis, cytomegalovirus retinitis, progressive multifocal leuco-encephalopathy and intestinal parasites. While the majority of IRIS events are infectious in nature, auto-immune IRIS reactions have also been described in adults.[8]

DISCUSSION

IRIS is a condition seen in some cases of AIDS or immunosuppression, in which the immune system begins to recover but then responds to a previously acquired opportunistic infection with an overwhelming inflammatory response that paradoxically makes the symptoms of infection worse.[9] It is thought that the immunopathological response initiated by HAART restores the immune response against pathogenic antigens.[10] There is paradoxical worsening of pre-existing infectious processes following initiation of HAART in HIV-infected individuals.[9]

These cases highlight the risks faced during immune reconstitution in adolescent and young adult patients who commence ART with advanced immunosuppression.

TABLE I. TABLE DISPLAYING AGES, ABSOLUTE CD4 COUNTS AND PRESENTATION TIME OF IRIS AMONG ADOLESCENTS/YOUNG ADULTS OVER 1 YEAR AT THE INFECTIOUS DISEASES INSTITUTE, KAMPALA

Age (yrs)	CD4 counts at initiation of HAART (cells/µl)	IRIS condition	Time from start of HAART to onset of IRIS (wks)
19	45	Pulmonary tuberculosis	4
20	77	Oral candidiasis	6
21	56	Kaposi's sarcoma	3
23	65	Herpes zoster	9
24	65	Cryptococcal meningitis	16
24	73	Oral candidiasis	6

CONCLUSION

IRIS occurs in adolescents and young adults, but little is known about IRIS in general and minimal research has been conducted in the adolescent/young adult age group.

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LETTER • LETTER • LETTER • LETTER

SANBS'S POLICY ON BLOOD DONATIONS FROM MEN WHO HAVE SEX WITH MEN

To the Editor: We at the South African National Blood Service (SANBS) are acutely aware of the issues surrounding the exclusion of men who have sex with men (MSM) from donating blood and the negative emotions that surround this policy. I would like to assure readers that SANBS does not make such decisions lightly, and we constantly review policies based on the latest scientific findings. It is perhaps time to review the basis of the current policy and engage in debate on its scientific merit.

It is, however, important to clarify a few misconceptions regarding our policies on the sexual activities of our donors.

In an editorial comment on 6 January 2010, the editor of *The Herald* newspaper in Port Elizabeth stated: 'A pattern of multiple partners or of unprotected sex ... is clearly also high-risk and yet heterosexual donors who may be sexually reckless are spared prying questions and the possible refusal of their offer of blood.'[1] This statement is factually incorrect. When donating blood, *all* donors, whatever their sexual orientation, have to answer very personal questions regarding their sexual activities during the preceding 6 months.[2]

Any person who has had any form of potentially high-risk sexual activity will be deferred for a period of 6 months following the high-risk activity. A donor who has multiple sex partners will be regarded as being at potentially high risk regardless of sexual orientation. At no point does SANBS suggest that high-risk sexual practices are exclusive to the gay community, hence the self-exclusion questionnaire's comprehensive set of questions regarding various sexual activities and practices.

There are over 450 rules guiding donor selection with

regard to medical conditions and lifestyle, and there are many groups of people whom we defer from donating, either temporarily or permanently.[3] Some individuals in these groups may have a very low risk of blood-borne infections and their blood would probably be safe to give to patients, but since it is impossible to identify specific individuals at low risk it is safest to ask everyone in the higher risk groups not to donate blood.

The request not to donate blood can be disappointing and frustrating to some people who wish to do so. Our decisions are based on information and research about the effects our policies on blood supply safety, not out of a desire to discriminate against any particular group.

The aims of donor selection are to:

- select donors whose blood is most unlikely to transmit any infection
- collect enough blood to meet patients' needs
- make sure that donors themselves come to no harm through the blood donation process.

We have to balance these three aims while keeping the selection process clear and simple, bearing in mind that almost a million units of blood are collected each year – a mammoth task complicated by stringent quality control and logistics.

The preliminary findings of recent studies among MSM, such as the JEMS study conducted in Johannesburg and Durban and the Soweto Men's Study, have found their HIV prevalence to be more than double the Actuarial Scientists of South Africa (ASSA)'s estimate of a 15.5% national HIV prevalence and the UNAIDS estimate of 18.1%.[4-8]

South Africa was one of the first countries in the world to lift the total ban on men who have sex with men donating blood. Other countries such as Sweden are only now starting to follow our example. We still have among the most progressive policies regarding MSM in the world, and while this may not be much consolation to gay men in stable relationships, it is testimony to SANBS's commitment to be as inclusive as possible with regard to the community we serve.

Internationally this is a very topical discussion. It is interesting to note that in the USA some politicians have called for the lifting of the ban against MSM donating blood and that this was countered by the Haemophiliac Society, a group whose members were severely affected by infected blood during the 1980s.

It is easy to get lost in all the numbers and emotions, but at SANBS we have the very tough responsibility of weighing up the right of an individual to donate blood against that of a patient to receive blood that is as safe as it is humanly possible to make it. The decision on which groups of the population will be or should be allowed to donate must be taken on the basis of scientific merit and the blood service's ability to implement policies that are clear and concise.

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ERRATUM

In 'Changes to the ART guidelines – an overview', which appeared on pp. 28 - 30 of the April 2010 issue of the *Journal,* the first sentence under the heading 'National regimens' and the heading to Table I should have read 'National regimens for adults and adolescents' and not 'National regimens for children and adolescents'. We apologise for these errors and have corrected them on the web version of the article, in which there are also other adjustments.

ORIGINAL ARTICLE

THE ROLE OF SOUTH AFRICAN TRADITIONAL HEALTH PRACTITIONERS IN THE TREATMENT OF HIV/AIDS: A STUDY OF THEIR PRACTICES AND USE OF HERBAL MEDICINES

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Background. A large proportion of HIV-positive South Africans regularly consult traditional health practitioners (THPs) for their health care needs, despite evidence of negative interactions with antiretrovirals (ARVs) and no published peer-reviewed clinical evidence for the efficacy of traditional medicines in the treatment of HIV. We investigated the dominant practices of THPs towards HIV-positive patients and whether these practices have changed following widespread public awareness campaigns covering HIV and its treatment.

Method. The study used a semi-structured interviewer-administered questionnaire in the home language of the interviewee. A total of 52 THPs from four provinces (Gauteng, Limpopo, KwaZulu-Natal and Eastern Cape) were interviewed. Of the respondents 38% were based in the rural areas, and 69% classified themselves as inyangas, the remainder being sangomas.

Findings. All the THPs in the survey offered treatment for HIV, although only 20% claimed to be able to cure the disease; 88% prepared their own medication, mostly from plant material, and sold their products as aqueous extracts in labelled bottles. None of these products had been systematically evaluated, and there was generally no record keeping, either of the patient or of the medicine itself. Quality control practices such as expiry dates, controlled storage conditions and batch records were totally unknown in our sample. Only 38% of the THPs had received training on HIV/AIDS, although 75% believed that they were well informed about the disease. Our own assessment was that only 50% had a working knowledge of HIV; more disturbingly, 37% believed that only traditional medicines should be used for its treatment and a further 50% believed that traditional medicines and ARVs can be taken simultaneously.

Interpretation. Despite ongoing public educational campaigns on HIV, some of which have specifically targeted THPs, the care of HIV-positive patients continues to be compromised by the traditional sector. Although some progress is evident, THP approaches to HIV treatment fail to conform to minimum standards proposed by the World Health Organization and other organisations, and represent a considerable challenge to the integration of THPs with the biomedical sector and the antiretroviral treatment programme in South Africa.

Arguments in favour of the incorporation of traditional health practitioners (THPs) into the overall health system are highly persuasive,[1,2] especially in the context of South Africa's HIV epidemic and the inability of the public health sector to cover the health care needs of all HIV-positive patients.[3] However, even those who support a more significant role for THPs have articulated a set of minimum standards that must be met as a pre-condition to this step, including:[2,4,5]

- the systematic evaluation of African traditional medicines (ATMs)
- the standardisation, processing and packaging of traditional medicines
- training on HIV to ensure a high level of prevention (of HIV) and care (of patients)
- the development of mechanisms to regulate the practice of traditional healing.

Over the past 3 years, Arvir Technologies, a public-funded company that was established to validate and register a herbal medicine for the treatment of HIV based on ATMs, have been working on the first of these standards, namely the evaluation of ATMs, and more specifically on three plant extracts the use of which for the treatment of HIV/AIDS by THPs has been reported previously.[6,7] This project has raised a number

of important questions about the curative approaches and practices of THPs, and the supply channels for the plant-based ingredients of their medicines, as follows:

- Several studies[8-11] have reported widespread consultation of THPs by people living with HIV/AIDS, reflecting a high level of trust in both traditional methods and ATMs; what is the basis of this support, and is there any evidence for the efficacy claims of THPs in their treatment of HIV (anecdotal or clinical)?
- The traditional health sector is known to be highly divergent; what are the dominant treatment approaches, and what are the trends in this regard?
- Regulation of the sector has recently been implemented through the promulgation of the Traditional Health Practitioners Act (No. 22 of 2007); to what extent has the Act changed the profile and conduct of the sector, and could this facilitate the introduction of a fully validated herbal medicine?
- Similarly, there have been several educational programmes to assist THPs to improve their understanding of the disease and their alignment with the goals of the antiretroviral (ARV) treatment (ART) programme in South Africa; have the programmes been successful in this regard?
- Allopathic and traditional medicines are typically seen as highly divergent; what is the level of interaction between the two sectors (biomedical and traditional health care), and are inter-sectoral referrals increasing?

In our research, we have attempted to answer these questions. The underlying intention was to develop an understanding of whether and how we could engage with the traditional health sector, and to define better approaches for improving the biomedical/traditional health interface.

METHODS

The study was undertaken using a semi-structured interview-administered questionnaire. It was conducted in four provinces of South Africa, and a total of 52 THPs were interviewed (Table I). The interviewees were identified by asking members of the community for information on the prominent THPs; once identified, the researcher explained the purpose of the study to the practitioner and requested permission for the interview.

TABLE I. DISTRIBUTION OF INTERVIEWEES BY PROVINCE

Province	No. of THPs participating
Eastern Cape	13
Gauteng	11
KwaZulu-Natal	15
Limpopo	13

The questionnaire covered a range of areas including membership of a professional association (as prescribed by the Traditional Health Practitioners Act), the extent of training on HIV/AIDS already completed (including treatment with ARVs), the level of knowledge about the prevention, incidence, diagnosis and biomedical treatment of HIV/AIDS, the number of HIV-positive patients being treated, interaction with the biomedical sector (referrals and diagnosis), and the nature of the THP's treatment for HIV (including quality control of prescribed medicines).

RESULTS

AN OVERVIEW OF THP PRACTICE AND HIV/AIDS

The majority of THPs (69%) in our study classified themselves as inyangas (herbalists); in other words, the source of their healing is considered to derive from their use of medicinal plants, as opposed to the approach of the sangomas (diviners), who rely more on divination for their healing approach. Diviners have different names in different regions of South Africa, depending on the dominant regional culture, including *izangoma* in Zulu, *amaggira* in Xhosa, *ngaka* in Northern Sotho and *mungome* in Venda, although the majority of South Africans refer collectively to this group of THPs as 'sangomas'.[12,13]

Except in the Eastern Cape and Gauteng (where the figure was only 50%), most of the THPs in this study (79%) were registered with a local THP association, although no practitioners were as yet registered in terms of the Traditional Health Practitioners Act (No. 22 of 2007). This and other observations lead to the inevitable conclusion that implementation of the Act since its promulgation has been almost non-existent in all regions of the country.

Not surprisingly, all the THPs in our study regularly see HIV-positive patients (between 3 and 10 patients per week). The THPs stated that most of their patients were women, but believed that males are the dominant transmitters of HIV/AIDS. In their view, the gender differences make it difficult to treat couples (either discordant or both HIV positive) because men do not talk openly about their HIV status and are therefore less likely to seek treatment.

TRAINING AND KNOWLEDGE OF HIV/AIDS

Only 38% of the THPs had received HIV/AIDS training of one or more days; as a result, their knowledge of the disease was limited and influenced by a high level of suspicion of non-traditional interventions and biomedical strategies. For instance, some THPs still believe that there is no such thing as HIV/AIDS and continue to associate the symptoms of the disease with cultural notions of sickness, e.g. *makgome* in Pedi and *isifusenhlu* in Zulu, which require the performance of

a cleansing ceremony for healing. In our assessment, which was based on answers to a standard set of questions about HIV, its treatment and its prevention, only 50% of respondents have a working knowledge of HIV, although 75% feel that they were well informed about the disease and its symptoms (Fig. 1).

Although limited in the sample, THPs' ignorance and mistrust of condom use as a prevention strategy is of great concern. Some opinions expressed in this regard were:

'In the past there were no such things as condoms or HIV in our society; ever since condoms were brought to us there is a high rate of HIV/AIDS because they are infested with diseases. Proof is in that oil lubricant.'

'Condoms are contributing to the spread of HIV/AIDS, for an example if you put condom in a sunny condition or pour hot water on it, you will notice worms coming out of that experiment. That is the very same worm they are referring to as AIDS.'

DIAGNOSIS AND TREATMENT

For the diagnosis of HIV, at least 69% of the THPs stated that they refer their patients to the biomedical sector for testing and require a positive HIV test result before the patient can start treatment (Fig. 2). The remaining practitioners use various approaches including THP observation, patient self-diagnosis and 'dreams and guidance from the ancestors'.

The modality of the treatment, even within the two separate groups of inyangas and sangomas, varied considerably. The latter often require patients to undergo a rigorous in-house cleansing and treatment routine. For instance, a THP in rural Eastern Cape, who sees HIV-positive clients from all over the country, has built a hospice in his yard for his patients. Inyangas, on the other hand, follow an approach of an initial consultation with fortnightly or monthly follow-up visits, depending on how quickly the prescribed treatments are completed.

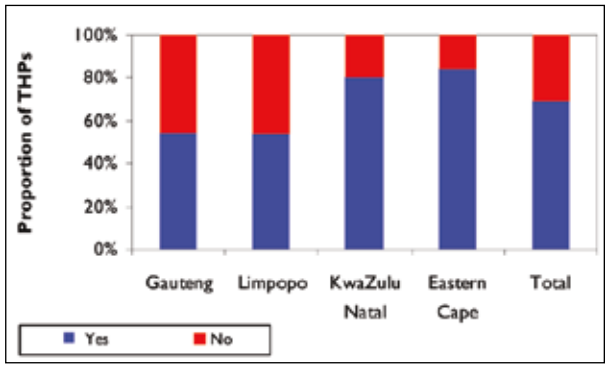

Fig. 2. THPs referring patients to clinics for HIV testing.

Of THPs in our sample 73% prescribe a herb-based solution called *imbiza* (Zulu) which is sold in a 2 litre or 750 ml bottle and is claimed to cleanse or purify the blood. It was apparent from the research that a wide range of plants collected from different geographical regions and ecological systems are used in the preparation of the *imbiza*. It is claimed that the practitioners' understanding of plant medicinal properties is based on an extensive knowledge of their traditional use, obtained from the ancestors and passed down through oral tradition. Almost all the THPs (88%) prepare their own medicine using the natural plant ingredients and a hot water infusion process.

The questionnaire specifically avoided detailed questions about the exact identity of the ingredients in order to protect any potential intellectual property. In some cases, however, this information was provided without any prompting and included a number of plants, the antiviral and immunomodulatory properties of which have already been reported.[7,14–17] The plants were sourced from the local area (collected personally by the THP) and also from markets trading in medicinal plants (mostly in the major urban areas).

The recommended dosage varies according to a number of factors, as follows:

- stage of the disease (chronic stage 125 ml 3 times a day; bed-ridden patients 250 ml 3 times a day)

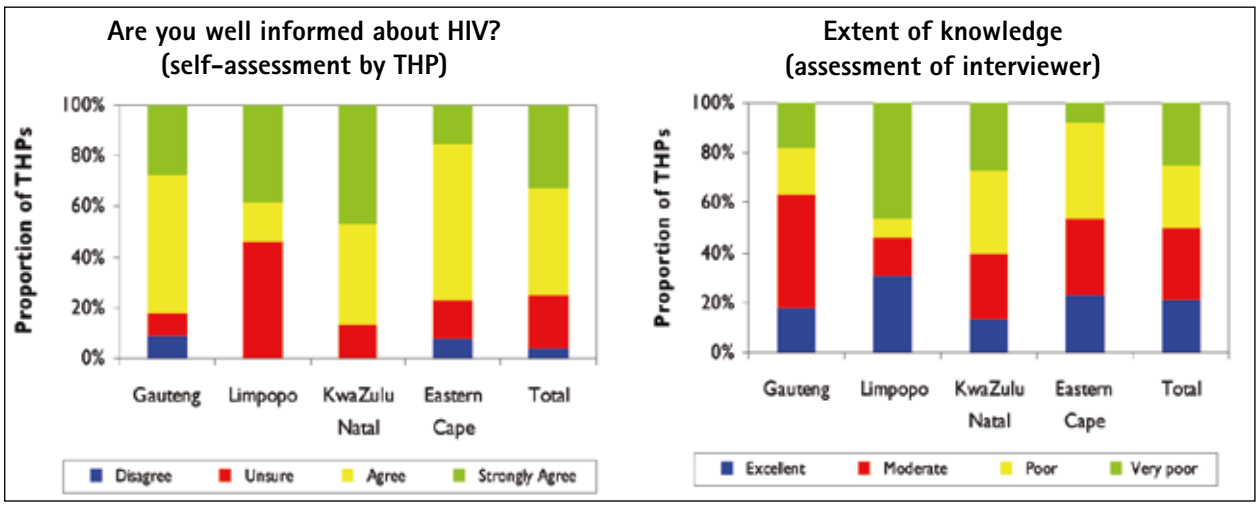

Fig. 1. Extent of knowledge (THPs and interviewer assessment).

- affordability to the patient (unemployed patients 3 times a day; employed patients 4 times a day)
- distance from which the patient comes (patients from far places are given a 5 litre bottle and take 60 ml of the medicine 3 times a day).

The cost of medicine also varies from a minimum of R200 to a maximum of R2 800 (Fig. 3). The treatment cost is determined by the following:

- the local reputation of the THP and hence patient belief in the efficacy of ATMs (the better the reputation, the more expensive the treatment)
- the variety of herbs used (the more herbs, the higher the price)
- the location of the practice (prices in the rural areas are generally lower).

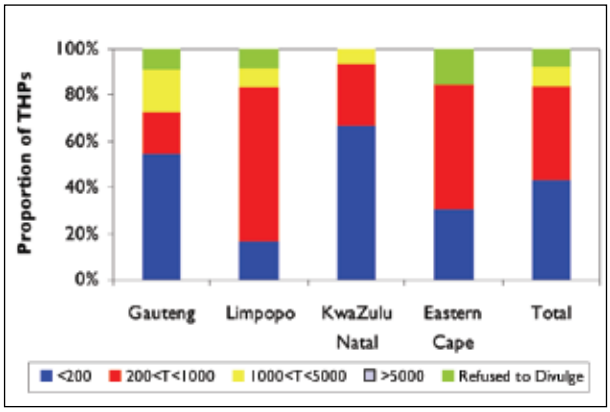

Fig. 3. Cost of traditional medicines for the treatment of HIV.

All the THPs in our survey were confident about the efficacy of their treatment for both HIV (20% claim to be able to cure HIV; the remainder to treat the infection) and HIV/AIDS-related opportunistic infections, although we were shown no recorded evidence for these claims. When asked to show evidence to support their statement, a number of claims were made including verbal reports of increases in CD4 count and patient well-being. As noted later, only 17% of THPs keep any patient records and track HIV status.

Based on our own research and the work of other drug discovery organisations, the basis for claims relating to most of the plants is highly questionable. This statement is supported by two main arguments derived from an extensive evaluation of the antiretroviral properties of plant extracts, as follows:[6]

- Most of the plant-based traditional medicines are prepared through hot water infusion of dried plant material (leaves, roots, bark, etc.); the resultant solutions contain at most 0.5% of extracted solids, so that a 250 ml dose in turn contains the equivalent of 1.25 g solid material. The concentration of the active ingredient(s) varies considerably depending on the plant itself and in many cases these ingredients have not been properly identified. However, our work with three local products indicates that the active ingredient(s) are at most 5% by mass of the total extract. In other words, a patient taking a 250 ml dose of a herbal infusion (the highest dose recorded in our study) will be consuming not more than 63 mg of active ingredient(s) per dose, or 188 mg per day.
- A wide range of specific antiretroviral activities for plant-based natural products (and other compounds) has been reported in the literature,[14-17] but even the most active natural compounds have activities no better than between 1 and 5 µM based on a range of *in vitro* cell-based assays. These values are between 100 and 1 000 times less active than the equivalent allopathic medicines such as zidovudine, efavirenz and tenofovir (Tables II and III). In other words, a patient taking a traditional medicine for the treatment of HIV will be receiving on average less than 0.5% of a therapeutic dose. This calculation does make some assumptions about the bio-availability of the natural product(s) but is a reasonable estimate of effective dose and its comparison with the registered antiretroviral products.

In summary, although many plant extracts have a measurable level of antiretroviral activity (as determined in cell-based assays), this activity is many times lower than that of the synthetic products. Considering that HIV patients on traditional medicines are taking on average less than 150 mg of the active compound(s), the net dose is only a fraction of the required therapeutic dose, and the possibility that a level of viral control is achieved is remote.

QUALITY CONTROL, EFFICACY AND PATIENT RECORDS

Most of the THPs (69%) claimed that their medication is of good quality and that there is no need for batch records, expiry dates or quality assessment of the ingredients/final product, which are standard concepts in the preparation of allopathic medicines. When asked to explain the reason for the difference, the THPs noted that 'unlike Western medicine our medicine doesn't have any preservatives; therefore there is no need to include expiry dates because natural plants don't expire'. In addition, very few THPs label their products.

In terms of patient records, as has been stated previously, only 17% of THPs keep any form of records, with the actual proportion varying from 26% in Gauteng to 8% in the Eastern Cape. As a result, no conclusive results can be derived from analysis of the treatment outcomes since these cannot be supported by documented evidence including health assessments, viral loads and other indicators of disease progression in HIV-positive patients. It is clear that this is one important area in which training can play a major role in upgrading the quality of care being provided by THPs in South Africa.

TABLE II. ANTIRETROVIRAL ACTIVITY AND ACTUAL DOSAGE OF SEVERAL SYNTHETIC PRODUCTS*

Drug name	Class	IC_{50} (µM)	TC_{50} (µM)	Therapeutic index	Dosage (mg/d)
Efavirenz	NNRTI	0.0015	80	53 333	600
Maraviroc	EI	0.001	25	20 161	600
Lamivudine	NRTI	0.07	360	5 143	300
Nevirapine	NNRTI	0.029	320	11 034	400
Stavudine	NRTI	0.03	100	3 333	60
Zidovudine	NRTI	0.002	32	16 000	600
Emtricitabine	NRTI	0.04	150	3 750	200
Tenofovir	NRTI	0.005	29	5 800	300
Indinavir	PI	0.014	32	2 286	1 600

*Data for all the synthetic and natural products have been obtained directly from the National Institute of Health's database,[18] which lists the anti-HIV activity of over 170 000 compounds based on information in the literature. Where possible the values for the PBMC assay have been used.

NNRTI = non-nucleoside reverse transcriptase inhibitor; EI = entry inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor.

TABLE III. ANTIRETROVIRAL ACTIVITY AND ESTIMATED DOSAGE OF SEVERAL NATURAL PRODUCTS*

Plant	Active ingredient	IC_{50} (µM)	TC_{50} (µM)	Therapeutic index	Estimated dosage (mg/d)
Syzygium claviflorum	Betulinic acid	1.4	13	9	60 000
Lobostemon trigonus[6]	Unknown (data shown for crude extract)	~2.5	2 000	800	150 000
Curcuma longa	Curcumin	5.0	10.0	2	100 000
Inula britannica	3,5-di-O-caffeoylquinic acid	2.0	486	243	40 000
Calophyllum lanigerum	Calanolide A	0.1	10	100	8 000

*Data for all the synthetic and natural products have been obtained directly from the National Institute of Health's database,[18] which lists the anti-HIV activity of over 170 000 compounds based on information in the literature. Where possible the values for the PBMC assay have been used.

INTERACTION WITH THE BIOMEDICAL HEALTH CARE SECTOR

When asked about the possibility of interaction with other health practitioners, THPs believed that nurses undermine their work and do not accept the efficacy of their treatment. As a result, THPs are reluctant to refer their patients to the biomedical sector for ART. A similar observation has been reported in other studies.[19]

The THPs indicated that unlike nurses and doctors they do not take the patients off ART but encourage their patients to take both ATMs and ARVs, since they believe that ARVs are also made from *muti* (Fig. 4). At least 50% of the THPs participating in our study showed little interest in learning or working with the biomedical sector and several openly criticised the allopathic approach, making statements such as 'doctors kill patients with their ARVs'.

DISCUSSION

The results of this study have shown that many THPs offer treatment for HIV/AIDS despite a somewhat limited understanding of the virus, the symptoms of infection and its treatment. Furthermore, the medicines are expensive relative to both patient incomes and the biomedical equivalents, have no recorded evidence of efficacy, and are not quality controlled in most respects.

Despite these factors, many patients continue to consult THPs for HIV-related illness and to use traditional medicines. The persistence of this support is due to many factors, including:

- an ongoing belief in the efficacy of traditional medicines, which is considered to have been passed down through generations from the ancestors

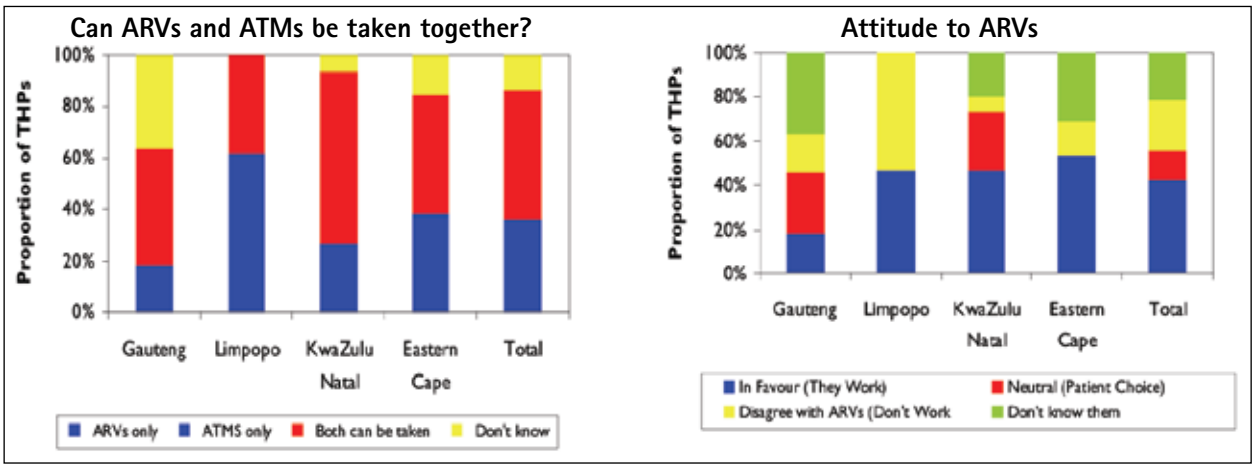

Fig. 4. THPs' attitudes to ARV treatment.

- considerable competition between the two treatment methodologies, especially by the THPs, who openly discredit the conventional sector in various ways (referral of a patient to the tertiary sector by a THP is in many respects a direct conflict of interest)
- the confidentiality of consulting a traditional healer (there is a belief that information such as the patient's HIV status is not secure in the biomedical sector)
- the perceived uncaring, unsympathetic and impersonal approach of the biomedical sector to patients, which is humiliating and hurtful to the patient; doctors are considered to give inadequate time to patient consultation
- the side-effects of ARVs and the fact that these medications are not a cure, but have to be taken forever
- lack of regulation in the sector, which encourages illegal and opportunistic practices including wild claims about treatment efficacy; in some cases the more bizarre the treatment, the greater the number of patients.

These problems are well known in the sector, and other authors have identified a set of minimum standards that require urgent implementation.[9] Our study has shown that little progress has been made with implementation of these standards. For instance:

- Although all of the THPs claim to treat HIV (and 20% to cure the disease), none of the treatments have been systematically evaluated.
- The majority (88%) of the THPs interviewed prepare their own medication but fail to keep patient records or batch data for each preparation. Most of the products are sold in labelled bottles as liquids, and none have any expiry dates on the labels. The opinion of the THPs is that plants do not expire; there is therefore no need for proper packaging or controlled storage conditions.
- Of the THPs in our sample, 38% have received training on HIV/AIDS and 75% believe that they are well informed about the disease; however, based on their replies to a few rudimentary questions about the disease, our assessment was that only 50% have a working knowledge of HIV.
- Perhaps more disturbingly, 37% believe that only ATMs should be used for the treatment of HIV and a further 50% believe that both ATMs and ARVs can be taken simultaneously.

It is apparent that many THPs play a role in HIV prevention and care by referring patients for HIV testing (69% of THPs), counselling patients with HIV and opportunistic infections, and distributing condoms to their patients (62% of the total). Our study makes it clear that this role is sub-optimal and could be improved through further training and regulation. Despite the fact that such regulation has recently been implemented by promulgation of the Traditional Health Practitioners Act, and that 79% of our sample of THPs were registered with a THP association, the Interim Traditional Health Practitioners Council of South Africa is not yet operational and there is no quality control in the sector or enforcement of the legislation.

With respect to capacity development of THPs, it is recommended that training in the following areas should be urgently addressed:

- an understanding of the HIV and the pathology of the disease
- the adoption of safe sexual practices and use of biomedical prevention methods
- quality control of traditional medicines, including concepts such as expiry and variability of raw materials
- the dangers of taking ATMs and ARVs together
- identification of symptoms of HIV infection to assist with counselling and treatment, including referral to the biomedical sector.

CONCLUSION

In conclusion, it will be a major challenge to use the THP network for distribution of a registered herbal medicine owing to ongoing ignorance regarding HIV, a high rate of illiteracy among THPs especially in rural areas, and local cultural beliefs that may prevent adoption of biomedical approaches. Nevertheless, the extensive network of THPs and ongoing confidence in their abilities within local communities suggest that efforts to address these challenges will be worthwhile.

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Conflict of interest. There is no conflict of interest for either author. The work was undertaken to understand the dynamics of the traditional health care sector in South Africa with respect to the treatment of HIV/AIDS, and to consider the suitability of this sector for the distribution of a herbal medicine. These objectives are clearly stated in the text of the article.

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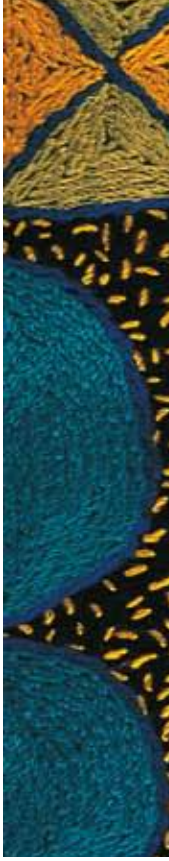

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ORIGINAL ARTICLE

PREVENTION IS BETTER THAN CURE – THE ART OF AVOIDING NON-ADHERENCE TO ANTIRETROVIRAL TREATMENT

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The much-used phrase 'prevention is better than cure' is applicable to many circumstances, including human immunodeficiency virus (HIV) infection. In recent years suggestions have been made for a move towards treatment strategies that emphasise prevention of foreseeable adherence problems on a patient-by-patient basis, through focused patient preparation before commencing antiretroviral therapy (ART). This is well elucidated in a statement made in 2004 by Coetzee *et al.*:[1] 'As it is difficult to ascertain robust predictors of adherence, there has been a move to concentrate on patient preparation before the initiation of ART rather than the use of non-clinical predictors of adherence or selection criteria. A paradigm focused on preparation rather than selection is better suited to the aggressive targets for the scaling up of ART in countries with large epidemics (such as in South Africa), where the view of ART as a very expensive rationed intervention is rapidly changing.'

Strategies for improving patient behaviour and enhancing drug adherence exist but are often complex, requiring much one-to-one patient counselling, and they are often implemented too late, once poor habits have already been established. More value may therefore lie in thorough preparation of patients before commencing ART, rather than adherence interventions once patients are already on treatment. This is not only because consistent and efficacious drug therapy is life saving, but also because drug-resistant strains of HIV emerge in the presence of sub-therapeutic dosing due to sub-optimal adherence.[2,3] The concept of 'prevention is better than cure' may therefore be applicable to the problem of non-adherence among patients on ART even more than in the management of chronic non-infectious diseases in which drug resistance is not an issue of concern.

We therefore undertook an analysis of results from the adherence monitoring in our HIV care and treatment programme to evaluate whether a change in the focus of conventional HIV treatment strategies would be effective in preventing non-adherence.

BACKGROUND INFORMATION ON THE HIV CARE AND TREATMENT PROGRAMME

Our programme, launched in 2003, is situated in Cato Manor, a ward of the eThekwini (Durban) Metro in KwaZulu-Natal, South Africa, which encompasses both low-cost housing and informal settlements and is notably an area of low income, with many households and families having no formal income generation.

At the end of November 2008 we had 1 238 patients enrolled in HIV care, with 499 of them on ART (436 adults and 63 children). The programme provides a patient-centred, rights-based, holistic approach to improving and maintaining the wellbeing of HIV-positive mothers, any of their infected family members, and uninfected infants less than 1 year of age. Mothers are generally the primary caregivers in a Cato Manor household, so improvement and maintenance of their health, despite HIV infection, benefits the entire family, as they remain productive and fully functional as caregivers and/or breadwinners. The programme views HIV as a communicable but manageable chronic disease that affects the whole family unit. With a view to keeping family units strong, HIV-positive household members of existing programme participants are eligible for enrolment into HIV care and treatment.

While the approach is to maintain good health before ART is indicated, once eligibility for ART is established patients are prepared, both medically and psychologically, for commencement of treatment according to World Health Organization (WHO) guidelines for the treatment of HIV infection. Medical preparation involves patient examination, evaluation of patient history, exclusion of current tuberculosis

(TB) infection, a full blood count, and kidney and liver function tests. Psychological readiness is assessed by trained HIV counsellors, who conduct drug readiness training before commencement of treatment. Drug readiness training is run over 3 weeks in small-group sessions and includes modules on positive living with HIV infection, preparation for appropriate administration of medicine and adherence to treatment regimens.

METHODS

MONITORING ADHERENCE

Adherence to treatment in adults receiving ART was monitored by pill count at scheduled clinic visits, and expressed as the percentage of the prescribed doses that had actually been taken since the previous visit. Data collected over a 1-year period (December 2007 - November 2008) were analysed monthly, as well as retrospectively at the end of the observation period. At each visit patients were questioned as to whether they were having problems with adherence. Problems with adherence that were identified for specific patients during the course of the year were dealt with at the time by implementing one-to-one adherence counselling, education regarding medication, and the use of any other appropriate aids for helping patients to adhere to treatment.

RESULTS

GENERAL PATIENT DETAILS

At the end of the observation period (end November 2008) there were 499 patients on ART (436 adults and 63 children). Of the adult group, 77 (17.7%) were male and 359 (82.3%) were female, and the mean age was 31.1 years (range 16 - 62 years). Patients had been on treatment in this programme for a mean of 21.2 months (range 1 - 69 months). Twenty-one of the adults on ART were transferred into the programme already on treatment, and had a mean CD4 cell count of 406.3 cells/µl on entry to the programme. The 415 treatment-naïve adults who were initiated on ART in our programme had a mean CD4 count of 141.5 cells/µl at initiation (range 0 - 675 cells/µl).

While paediatric adherence monitoring was done at each visit, only results for the adult cohort were included in this analysis, as the number of children in the programme was comparatively small.

ADHERENCE TO TREATMENT

Analysis of pill count data showed that the mean adherence for every month throughout the year was above 94% and the mean adherence for the patient cohort over the entire observational period was 96.4% (standard deviation (SD) 6.7%), with 90% of patients achieving adherence of 90% or more and 78.5% achieving adherence of 95% or more.

TREATMENT FAILURES AND MORTALITY

During this study (since 2003) 593 patients have been started on ART and there have been 6 treatment failures (1%), necessitating switching of patients to second-line regimens. Thirty-nine patients on ART have died while enrolled in the programme. Two deaths were due to injuries unrelated to ART and were therefore excluded from the deaths for the purposes of this analysis. Thirty-seven deaths were due to opportunistic infections or other HIV-related diseases. None of the patients who died had suffered a known virological treatment failure before death and any changes to the regimen were of single drugs, due to pregnancy, drug toxicity or contraindications. More than half of the deaths occurred within the first 3 months of starting treatment (51%) and 73% within the first year, suggesting that a prominent factor contributing to death was late presentation at the clinic with advanced disease.

EFFECTS OF ADHERENCE INTERVENTIONS AND MONITORING

Mean adherence values for the patient cohort increased throughout the observation period, with the lowest mean adherence (94.2%) reported in the 2nd month of adherence data collection, and the highest (97.4%) in the 11th month. Additionally, the percentage of patients on ART who returned their unused medicine at clinic visits increased each month during the observation period, as patients became more aware of the importance of returning medicine at each visit.

DISCUSSION

It is considered that a 95% adherence rate is required for sustained viral suppression in patients taking protease inhibitor (PI)-based regimens.[4,5] The mean adherence reported here indicates that medication-taking behaviour for currently used antiretroviral drug regimens was acceptable.

Our programme compares favourably with other studies that report mean adherence measured by medicine returns. A recent South African study in children reported 79% of patients achieving adherence of 90% or more, measured by pill count,[6] and data from a Botswana study in adults suggested this figure to be 74.4%,[7] compared with 90% for patients in this programme. A 2003 South African study of HIV-positive adults reported that 63% of patients were 90% adherent or better, while the mean adherence for the patient cohort was 87.2%.[8] Considering the percentage of patients achieving 95% adherence or more, a large public sector antiretroviral treatment programme in Zambia reported 62.9% of patients with such adherence,[9] more than 15% lower than the 78.5% of patients in our programme cohort. Two studies on HIV-positive adults in Kenya and Uganda reported similar adherence rates to those achieved in our programme, with 86.1% of patients in standard care achieving 95% adherence or more in the Kenyan

cohort[10] and 87 - 94% (measured at different time points) achieving 95% adherence in the Uganda study.[11] Both these studies used medicine returns as well as self-report methods of monitoring adherence.

The favourable adherence values measured over the observation period are evidenced by the low number of treatment failures of first-line ART regimens, and therefore only very few patients being switched to second-line treatment strategies (6 out of 593 patients). Adherence has been shown to have a direct impact on virological suppression[4,7] and therefore on treatment success, and this is reflected in the positive patient outcomes seen in this programme.

We observed an increase in mean adherence values for the patient cohort throughout the observation period. This improvement in mean adherence correlated with patients' compliance with instructions regarding clinic visits and tablet returns. The mere practice of requesting that unused tablets be returned, and the consistent questioning by pharmacy staff concerning such unused tablets if they are not returned, raised adherence as a point of discussion with patients, resulting in improved patient interaction and better understanding regarding the importance of adherence. The pharmacy staff were given opportunities to discuss specific issues affecting adherence that patients reported when questioned regarding their unused medicine. During the collection of data for adherence measurement, other social and psychological issues surrounding the issue of adherence were identified.

Our data showed that adherence behaviour of patients who returned unused medicine 50% of the time or more (i.e. 6 out of 12 months or more) was better than for those patients who only returned medication at less than 6 visits. Although the difference between the mean adherence for these two groups of patients is not statistically significant, the data may provide a useful tool for highlighting potential adherence problems, as well as a possible area of further research. Pharmacy refill adherence (measured as the percentage of expected pharmacy visits filled) has been shown to predict viral load suppression.[12]

The extended time patients spend in the programme before starting lifelong treatment provides an opportunity for them to observe other patients who are starting treatment, and those who are thriving on ART, which reinforces the trust that is built up over several clinic visits and repeated interactions with programme staff. While still physically well, patients have time to work with counsellors towards accepting their HIV status and adapting their lifestyle to accommodate necessary routines, tasks and habits that will enhance their health, including disclosing their HIV status to family and/or household members. It is during this time that they become practically and emotionally prepared for starting treatment over the long term. Time to accept their HIV status is important for achieving preparedness for starting ART, and for maintaining good adherence over the long term.

This approach to treatment would be applicable to large-scale implementation in ARV roll-out programmes in resource-poor settings because the staff required to implement the preparative interventions in this programme are at the lay counsellor level. Expansion of the lay counsellor quota of a multidisciplinary team will add less of a financial burden on programme resources than would an increase in clinical staff. Additionally, the employment and training of such lay people provides employment and empowerment to people who live in the community that the programme serves. Employing local residents as lay counsellors enhances knowledge of the community, as well as access into the community and surrounding area, which helps in dealing with difficult patient and family situations through home visits and identification of patients who would otherwise be considered lost to follow-up.

On the basis of our results we conclude that preventing non-adherence is a better treatment approach than strategies in which the primary focus is on identifying and rectifying non-adherence once it has been established. We therefore recommend that HIV care and treatment facilities include such preparative approaches for promoting adherence into their treatment programmes.

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ORIGINAL ARTICLE

PREVENTION OF MOTHER-TO-CHILD TRANSMISSION OUTCOMES IN THE PRIVATE SECTOR IN CENTRAL DURBAN

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The prevention of mother-to-child transmission (PMTCT) programme in the central region of Ethekweni Metro, KwaZulu-Natal (Durban central area), was investigated. Data for all HIV-exposed infants from eight private paediatric practices seen between January 2004 and June 2005 were reviewed retrospectively. One hundred and one black African infants were born to 100 HIV-positive women of average age 30 years. Median viral loads and CD4 counts were 11 391 copies/ml and 426 cells/µl, respectively. Eighty-six women received HAART and 5 had no prophylaxis. Of the 92 infants tested, 2 were HIV positive, giving a transmission rate of 2.2%. Both their mothers had received suboptimal prophylaxis, and if they are excluded, the transmission rate falls to less than 1%, a rate consistent with those in the developed world.

Effective prevention of mother-to-child transmission (PMTCT) strategies are known to reduce the incidence of paediatric HIV infection.[1] A small non-governmental project at McCord Hospital in Durban, KwaZulu-Natal, with access to highly active antiretroviral therapy (HAART), reported vertical transmission of 2.9%. The authors of that paper also reported results of two studies in the public sector, in 2002 and 2006, respectively, where transmission rates of 8.7% and 20.8% were achieved with a PMTCT drug regimen comprising single-dose nevirapine (sdNVP).[2] These were in Gauteng and KwaZulu-Natal respectively, while in the Western Cape in 2003 a rate of 8.8% was recorded for women given dual therapy of zidovudine (ZDV) from 34 weeks and sdNVP.[3]

In the private sector, many patients belong to medical scheme-funded disease management programmes, such as Aid for AIDS (AfA). PMTCT guidelines for developed countries, where HIV-infected newborns are becoming uncommon, are followed.[1,4] The programme comprises prenatal HIV-1 counselling and testing, and HAART (irrespective of CD4 count) from the second trimester onwards, unless the mother is already on antiretrovirals or fulfils the criteria for starting HAART immediately. Elective caesarean section, together with intrapartum intravenous ZDV, is offered and ZDV is given to the neonate. Formula feeding is supplied for 6 months and breastfeeding is avoided.

While many private practitioners follow AfA guidelines, they may use different regimens, depending on cost considerations. The present study aimed to investigate the outcome of infants born to HIV-positive mothers managed in a group of private paediatric practices in central Durban, KwaZulu-Natal.

METHODS

Ethical approval for this retrospective chart review was obtained from the Biomedical Research Ethics Committee of the Nelson R Mandela School of Medicine (Reference number BE047/47). Of the 20 paediatricians in the Durban Central region, 4 (20%) did not respond. All charts of HIV-exposed infants born between January 2004 and June 2005, from the 8 paediatricians who agreed to participate, were included. Data were collected by means of previously piloted questionnaires.

RESULTS

One hundred and one charts were available, of which 50 came from a single practice (which is an HIV referral centre). The balance was contributed approximately equally by the remaining practitioners.

One hundred and one infants (one set of twins) were delivered to 100 black African women, 93 by caesarean section. Fifty infants were boys, 20 were low birth weight, 2 were large for gestational age and 79 were appropriate for gestational age. Ninety-seven mothers were medical scheme beneficiaries (86 contracted to AfA). The mean age was 30 (range 18 - 44) years and mean parity was 1 child (range 1 - 4). Presentation and antenatal care initiation were in the first, second

and third trimesters for 40%, 34% and 26% of mothers, respectively. HIV infection had been diagnosed in the current pregnancy in the majority (75%) of cases, and the rest already knew their status.

Viral load and CD4 count measurements were recorded for 86 and 91 women, respectively. The median CD4 count was 426 (intraquartile range (IQR) 244 - 613) cells/µl. Only 13% of the women had CD4 counts less than 200 cells/µl. The median viral load at first presentation was 3.97 (IQR 1.6 - 5.8) logs or 11 391 (IQR 2 013 - 41 502) copies/ml.

Eighty-six women (86.0%) received HAART. This comprised ZDV and lamivudine (3TC), either together with lopinavir/ritonavir (if the CD4 count was >250) or together with NVP if the CD4 count was <250. The regimen also included intrapartum intravenous ZDV. Nine women did not receive HAART; 7 received only intrapartum intravenous ZDV, 1 had only intrapartum NVP, and 1 had dual therapy with ZDV/3TC. Treatment was initiated at less than 28 weeks in 32 women and between 28 and 34 weeks in 41 women. Five women received no prophylaxis because they presented for antenatal care very late in the third trimester.

All infants were formula fed and received ZDV for 6 weeks. Haemoglobin (Hb) measurements in 98 patients revealed 18 (4 preterm) with anaemia. Seventy-nine infants received PCP prophylaxis. There were 18 preterm infants, half of whom were born to women with low CD4 counts who received NVP as part of their HAART. Five and 3 of the premature infants were born to mothers who had received protease inhibitors and no prophylaxis, respectively. One of the latter 3 seroconverted.

Eight infants defaulted follow-up and 1 died (of unknown cause) at 5 weeks before testing was possible. Ninety-two infants were tested, 61 of them by polymerase chain reaction (PCR) at 6 weeks. Fifty-six were tested by enzyme-linked immunosorbent assay (ELISA) at 18 months (some of whom had already had a first PCR). Two infants were diagnosed positive, and their details are set out in Table I.

TABLE I. DETAILS OF THE 2 HIV-POSITIVE INFANTS

	Infant 1	**Infant 2**
Birth weight (kg)	2.2	3.0
Gestational age (wks)	33	38
Health at birth	Congenital pneumonia, anaemia	Well
Treatment	ZDV for 6 weeks	ZDV for 6 weeks
	Mother 1	**Mother 2**
Age (yrs)	28	37
Mode of delivery	Caesarean section	Caesarean section
Diagnosis of HIV	2 - 3 years earlier	During current pregnancy
ART prophylaxis	None	HAART initiated 5 days before delivery
Intrapartum IV ZDV	Yes	Yes
Viral load at delivery	Not recorded	50 000 copies/ml
CD4 count at delivery	Not recorded	327 cells/µl

DISCUSSION

Although our transmission rate of 2.2% appears better than the 2.9% from the McCord experience, the proportions of women in that group with low CD4 counts and receiving HAART were double and half, respectively. Our rate was not as good as the situation that pertains in the USA and Europe, where HIV-infected newborns are becoming uncommon, but is close to the 1 - 2% transmission expected for women from socio-economically advantaged areas in Africa who can safely formula feed.[1]

The mothers of both positive infants had suboptimal PMTCT, and if these women are excluded the transmission rate falls to less than 1%. In fact, in those women who were fully compliant there was no transmission.

One of the 2 mothers had been diagnosed 2 years before the pregnancy and presented for antenatal care but was not on medical aid and could not afford HAART. It had been planned to initiate HAART at 34 weeks, but she went into labour at 33 weeks. The other mother was diagnosed early in the current pregnancy but did not return for results, so HAART was initiated only 5 days before delivery. Non-adherence is a risk factor in perinatal transmission, but it is a problem with which even a developed country like the UK is grappling.[5]
Our study has confirmed the success of an appropriate PMTCT programme and the importance of prophylaxis and adhering to the protocol.

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FROM THE EDITOR

The wonderful World Cup and a devastating public sector strike are behind us. One generated national pride and reminders that we are the rainbow nation with fabulous potential, and the other national shame that compassion and humanity for the most poor and vulnerable could be sacrificed for material gain. With the enormous responsibility of lifelong antiretroviral treatment for over a million individuals we need a health system that is reliable, responsible and obsessive. The concept that health facilities would not be open, or worse still that patients would be barred from accessing those services, flies in the face of all our hard-won battles for adherence to pills and programmes. You may have seen the *Economist* of 9 August 2008, featuring an article referring to global ART programmes, from which I quote: 'as a result, taxpayers are accumulating an indefinite – and indefinitely growing – responsibility of keeping people alive'. Many First-World taxpayers have been generous in helping to expand and sustain our treatment programme – but following international news reports of treatment interruptions as a consequence of the strike, some of them may well be questioning our own commitment to that responsibility.

We have a clinically focused edition for you this quarter! Cassim and colleagues re-ignite the hope that we can eradicate paediatric HIV in South Africa with a report on the outcomes of HAART-based PMTCT in the private sector in KZN. Kwaan and colleagues, also from KZN, report on adherence strategies in a treatment cohort in Cato Manor. They emphasise simple strategies such as tablet return as a way to encourage dialogue with patients about pill taking. An interesting paper describes traditional healer beliefs and practices around HIV and ART, and interactions between biomedical and traditional health care. It seems that we still have a long way to go in terms of the two sectors really understanding each other's role. Ugandan colleagues present data on the immune reconstitution inflammatory syndrome among adolescents – numbers are small, but it is a point well made. This age group typically presents us with adherence challenges above those in adult and paediatric care, and treatment experiences that may be unpleasant need careful handling if we are to keep our adolescents adherent. Polly Clayden and co-authors summarise what we know (and do not know) about efavirenz in pregnancy. Two clinical case studies of gastro-intestinal mycobacterial infection follow, expertly commented on by Andrew Black from Baragwanath Hospital. One is from Pretoria, the other all the way from Taiwan, where HIV is really only just emerging. Many will feel a sense of foreboding or *déjà vu* as authors Kao and Hung make a plea for thinking of HIV co-infection in patients with extra-pulmonary TB. Two clinical cases of well-known opportunistic infections occurring in strange places follow. The first, again from Uganda, is a case of toxoplamosis of the hard palate, and the second *Pneumocystis jirovecii* in the external ear canal. Finally, Mitha and colleagues describe an unusual manifestation of lipodystrophy, namely multiple subcutaneous lipomas, which I hope will stir up interest and invite some comment. Finally, we have a letter from the Blood Transfusion Service. This section of the journal could do with much more traffic!

The *Journal* office has been offered some additional editorial help, which should enable more efficient management of your copy. Thanks to all who have been so patient. I am sure you will see a difference soon.

LINDA-GAIL BEKKER
Editor

MESSAGE FROM THE EXECUTIVE

The Society is about to embark on some of the most profound changes in its history. An external objective evaluation has pretty much told us what we knew – that we are too big and successful to continue with the current structure.

The Executive met for 2 days in April, to study the evaluation and suggest changes. Many of these are simply improved corporate governance – tightening up our legal, oversight and financial systems, tackling our voting systems (traditionally, only doctors could vote), the structure of the Executive, how we administer our branch meetings, providing more support to nurses, creating committees to handle specific projects and areas of works, updating our IT and data systems (non-paid-up members: be afraid) – all sensible stuff any organisation needs to do as it moves out of adolescence.

It is an exciting time. But we'll keep giving you the *Journal, Transcript,* the discussion fora, the branch meetings, more guidelines, the new nursing journal, the skills workshops, support for bursaries and an updated website – all the stuff that makes us good and wholesome.

FRANCOIS VENTER
President

SEPTEMBER 2010

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Cover: *Archbishop Desmond Tutu blew the vuvuzela at the Kethupila Youth Centre roof wetting ceremony in Masiphumelele on 2 July (picture by Dr Nienke van Schaik from DTHF). Elsewhere in this issue, the Archbishop is seen celebrating the Desmond Tutu HIV Foundation's Tutu Tester's first birthday with the staff after testing for HIV himself (p. 36). He emphasised the need for all South Africans to know their HIV status. And Tannie Evita said the same to visitors to the Voorkamerfest in Darling (p. 38). She publicly tested for HIV and encouraged everyone to practise safe sex.*

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