FROM THE EDITOR

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Happy reading and every best wish for a restful and peaceful festive season from the whole editorial team. See you next year!

LINDA-GAIL BEKKER
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It has been estimated that South Africa is home to more than 200,000 traditional health practitioners (THPs) and that such persons are consulted by more than 70% of the country's population. Given this situation, UNAIDS has recognised that THPs can play an important role in HIV/AIDS treatment programmes, and attempts have been made to integrate THPs into tuberculosis treatment and HIV/AIDS prevention programmes in South Africa. In respect of the latter, THPs in Inanda, Durban, for example, have attended formal training on HIV rapid testing which reportedly has resulted in the healers referring family members and subsequently clients for HIV testing and counselling. Despite receiving such training, the THPs do not seem to carry out HIV rapid testing themselves. This may be due to uncertainty about the legal and ethical implications of THPs conducting HIV testing.

International guidelines on HIV testing stipulate that only certified persons should perform HIV testing. Current South African policy does not stipulate who may perform an HIV test and is silent on an HIV tester certification process. Despite contradictions in national guidelines and policies on who may perform HIV testing, draft regulations allow for designated professionals and a 'competent person' to draw blood. While traditional health practitioners may be deemed competent persons, they are forbidden from performing such procedures by their governing statute. Accordingly, while it could be argued that it is ethically permissible for traditional health practitioners to perform HIV testing provided such persons are appropriately trained and certified, the performance of such procedures by such persons may have legal implications.

National policies must be established for the use of HIV rapid tests. Issues to be addressed include (italics added for emphasis):

- Personnel issues. Who will be allowed to perform HIV rapid testing, and what training and certification will be required? How will appropriate supervision be provided?
- Legal requirements that might apply to testing. Examples include country requirements for existing personnel certification as well as existing national laboratory and safety standards.
- Confidentiality issues.
- A strategic plan for implementation of HIV rapid testing should be developed. This plan will include provision for training of personnel and for continuously monitoring and improving the testing process.
- Local management (at site level) must ensure that all testing is performed by staff who are trained and certified according to the national requirements. The quality officer must also have a plan for evaluating the competence of personnel performing testing, both initially and on an ongoing basis at appropriate intervals. If there is no national certification programme, local management must ensure that staff are trained and are competent to perform HIV testing.
rapid tests according to these guidelines or national requirements.

In its 2007 guidance on Provider-initiated HIV Testing and Counselling in Health Facilities the WHO recognised that (italics added for emphasis):

... a redistribution of health worker responsibilities (task-shifting) in health facilities may help to overcome chronic staff shortages in some settings. This may entail identifying appropriately skilled lay personnel who can receive training and remuneration to carry out HIV testing and counselling activities under the supervision of health care professionals with more specialized expertise. People living with HIV/AIDS, AIDS service organizations and other community-based organizations and civil society groups can provide an important source of skilled lay personnel. In some settings, expanding the types of health workers who are authorized to carry out HIV testing and counselling, including rapid HIV testing, may require a review of local laws and regulations.

Given the WHO’s support for expanding HIV rapid testing, the WHO and US Centers for Disease Control and Prevention (CDC) have published a rapid testing training package. Among other subject matters the training covers assuring quality of HIV rapid testing, safety at the HIV rapid testing site, inventory management, quality control, blood collection and handling, documents and records, professional ethics, and blood collection by fingerprick. With regard to recommended certification criteria the training programme recommends:

- Successful completion of workshop
- Daily attendance of training
- Passing score of 80% on written post-test
- Passing score of 100% on final practical examination
- 100% accuracy of first 50 specimens tested under direct supervision.

Given the above guidance, it is important to consider whether South Africa has put in place relevant laws and policies to govern HIV testing and whether these allow THPs to perform such procedures.

LAWS AND POLICIES ON HIV TESTING IN SOUTH AFRICA

In 2000 the South African government published, among others, the Draft National Policy on Testing for HIV and Guidelines on Rapid HIV Testing. Neither document specifies who is authorised to perform an HIV test. In this regard, the draft National Policy on Testing for HIV simply refers to (italics added for emphasis) ‘the person administering the HIV test’, while the Guidelines on Rapid HIV Testing stress that ‘adequate training and experience is necessary before health care workers use these tests.’ An important issue to determine is what constitutes a ‘health care worker’.

According to the country’s pre-eminent statute governing health, the National Health Act of 2003, ‘health care personnel’ means health care providers and health workers, while ‘health care provider’ means a person providing health services in terms of any law, including in terms of the Allied Health Professions Act, 1982 (Act No. 63 of 1982); the Health Professions Act, 1974 (Act No. 56 of 1974); the Nursing Act, 1978 (Act No. 50 of 1978); the Pharmacy Act, 1974 (Act No. 53 of 1974); and the Dental Technicians Act, 1979 (Act No. 19 of 1979). In terms of the National Health Act, a ‘health worker’ means any person who is involved in the provision of health services to a user, but does not include a health care provider. If these terms are taken at literal face value and if ‘health care workers’ (the term used in the rapid HIV testing policy) is equated to ‘health workers’, it would mean that health personnel such as physicians, nurses and pharmacists would not be entitled to perform HIV rapid testing on patients as their designation, ‘health care providers’, is distinct from ‘health care workers’ and they are not mentioned in the guidelines on HIV rapid testing. This is obviously untenable and appears to be an oversight on the part of the drafters of the National Health Act and the guidelines on rapid HIV testing. In practice, HIV testing in South Africa, including the performance of HIV rapid testing, is performed by physicians, nurses, pharmacists and registered phlebotomy technicians, all of whom are governed by professional councils (and are classified as ‘health care providers’).

The National Health Act empowers the Health Minister to make regulations regarding the withdrawal of blood from living persons. In January 2007 the government published for comment draft regulations governing the use of, among others, blood and tissue. The draft regulations define a ‘competent person’ as meaning, in the case of the intravenous withdrawal of blood, a person registered in terms of the Health Professions Act, 1974 (Act No. 56 of 1974) as a medical practitioner or in terms of the Nursing Act, 2005 (Act No. 33 of 2005) as a nurse, or in the case of intra-arterial withdrawal of blood, a medical practitioner registered as a specialist in the procedure; in the case of a finger prick for the withdrawal of a drop of blood for testing purposes, a person mentioned in paragraph (a) or any person who has been trained to perform such a procedure (italics added for emphasis). There is currently no government-issued guideline in South Africa on HIV testing training or certification or any endorsement from government of the WHO guidelines on HIV testing training and certification outlined above.

Even though neither of the Councils that govern physicians and nurses has issued guidelines for HIV testing training, both Councils have issued generally
The ethics.indd   8

African Pharmacy Council (SAPC) stipulates that: perform such a procedure the draft regulations, they may have 'person to perform finger pricks as, in the words of counsellors could meet the definition of a 'competent Act, it could be argued that appropriately trained lay individuals is a matric (Grade 12) certificate with biology, to 'be equipped, through knowledge and skills gained, to safely collect blood and other human tissue samples for medical pathology or blood transfusion purposes.'17 In its guidelines on Good Pharmacy Practice, the South African Pharmacy Council (SAPC) stipulates that:

(a) Pharmacists who want to perform HIV antibody testing have to ensure that they have adequate training, knowledge, and skills to perform HIV antibody tests, interpret the results to counsel patients being tested.

(b) Every pharmacist who wants to do HIV antibody testing must be a trained HIV counsellor. Such training is provided for example by AIDS training and information centres.18 Lay counsellors are not governed by a professional association and their involvement in HIV testing programmes has been largely limited to HIV counselling and HIV test referral. One notable exception is the Perinatal HIV Research Unit (PHRU), which has an ongoing training programme for voluntary counselling and testing (VCT) testers. After receiving relevant training, the counsellors are placed in antenatal clinics in Soweto and perform HIV testing on clients.19 The selection criterion for such individuals is a matric (Grade 12) certificate with biology, and counselling experience. Although lay counsellors are not members of any of the abovementioned professions, in terms of the draft regulations of the National Health Act, it could be argued that appropriately trained lay counsellors could meet the definition of a 'competent person to perform finger pricks as, in the words of the draft regulations, they may have 'been trained to perform such a procedure.'16 It is not known whether the HIV rapid testing training programmes of the PHRU or the 'AIDS training and information centres' referred to by the SACP adhere to the HIV training guidelines and certification process published by the WHO. Regardless, this raises the question of whether appropriately trained traditional health practitioners could similarly be deemed 'competent persons' to perform HIV testing or finger pricks for HIV rapid testing.

LAWS GOVERNING TRADITIONAL HEALTH PRACTITIONERS

In 2004 parliament passed the Traditional Health Practitioners Act.20 It was assented to by the State President on 7 February 2005, and certain provisions of the Act became operational by proclamation on 16 January 2006.21 The constitutionality of the Act was soon challenged by Doctors for Life International (DFL) on the basis of insufficient public consultation. In August 2006 the Constitutional Court ruled in favour of DFL, declaring the Traditional Health Practitioners Act unconstitutional (along with three other statutes passed by parliament).22 The Court found that there had been insufficient or unreasonable levels of public participation at provincial level on the statutes in question. The Court's order invalidating the statutes was suspended for a period of 18 months to enable parliament to re-enact these statutes in a manner that is consistent with the Constitution. In 2007, after a period of further public consultation, parliament re-enacted the Traditional Health Practitioner's Act23 and the Act was assented to by the State President on 8 January 2008.

In terms of the Act 'traditional health practice' means the performance of a function, activity, process or service based on a traditional philosophy that includes the utilisation of traditional medicine or traditional practice and which has as its object:

(a) the maintenance or restoration of physical or mental health or function; or

(b) the diagnosis, treatment or prevention of a physical or mental illness; or

(c) the rehabilitation of a person to enable that person to resume normal functioning within the family or community; or

(d) the physical or mental preparation of an individual for puberty, adulthood, pregnancy, childbirth and death,

(italics added for emphasis) but excludes the professional activities of a person practising any of the professions contemplated in the Pharmacy Act, 1974 (Act No. 53 of 1974), the Health Professions Act, 1974 (Act No. 56 of 1974), the Nursing Act, 1974 (Act No. 50 of 1974), the Allied Health Professions Act, 1982 (Act No. 63 of 1982), or the Dental Technicians Act, 1979 (Act No. 19 of 1979), and any other activity not based on traditional philosophy.

In terms of the Act 'traditional philosophy' means 'indigenous African techniques, principles, theories, ideologies, beliefs, opinions and customs and uses of traditional medicines communicated from ancestors to descendants or from generations to generations, with or without written documentation, whether supported by science or not, and which are generally used in traditional health practice'.

HIV rapid testing is an activity not based on 'traditional philosophy' and constitutes the professional activities of the professionals governed and contemplated in the above-listed Acts. Accordingly, it would appear that THPs
are legally precluded from performing HIV rapid testing by their governing Act.

SUMMARY AND CONCLUSION

Current national policy and statutes appear to be in contradiction in respect of who may perform an HIV test (‘the person’ v. ‘health workers’ v. ‘health care workers’ v. ‘health care personnel’). However, the guidelines on rapid HIV allow ‘competent persons’ to perform HIV rapid tests. A traditional health practitioner may arguably be deemed a ‘competent person’ to draw blood or perform finger pricks for the purposes of rapid HIV testing provided they receive appropriate training to do so. In such an event, their involvement in HIV testing may arguably be ethically permissible (provided they do not use the testing process to peddle untested and potentially unsafe substances). The legality of doing so is, however, questionable.

The only legislation that governs THPs prohibits such persons from performing the professional activities of, among others, physicians, nurses, phlebotomists and pharmacists (all of whom may perform rapid HIV testing as part of their duties). Moreover, THPs are forbidden to perform procedures that are not based on ‘traditional philosophy’. Rapid HIV testing is not based on ‘traditional philosophy’ and so constitutes a forbidden activity for THPs.

Notwithstanding the potentially significant impact THPs could have on scale-up of HIV testing and VCT, it is recommended that THPs not be trained to perform HIV rapid testing as doing so:

(a) could be seen to be acting against the spirit, purport and intent of the legislature; and

(b) would be in violation of the Traditional Health Practitioners Act.

Even if the Traditional Health Practitioners Act is amended at some point to allow THPs to perform HIV testing, training and certification should be in accordance with WHO recommendations, as highlighted above. Such testing should also be performed under the supervision of health care professionals with more specialised expertise, in line with WHO recommendations highlighted above. This may allay concerns that THPs may attempt to use the HIV testing process to peddle their own untested remedies on clients.

REFERENCES


The use of mobile phones in South Africa has increased rapidly and they have become more affordable and available to an increasingly wider population. Their widespread availability has given them the potential to revolutionise health care communication and improve health services. Even before the phone became truly mobile, Haynes et al. found that communication efforts (e.g. telephone contacts) that kept the patient engaged in health care may be the simplest and most cost-effective strategy for improving adherence to chronic medication.1 Mobile phones can now be used to provide appointment reminders, create treatment adherence systems, record patient diaries, conduct risk assessments, provide information and even conduct research. This article reviews some of the many benefits and functions associated with mobile phone use and health management.

Mobile phones make it easier for health professionals and patients to stay in contact. In addition to their use for staying in touch, mobile phones can be used as tools to increase the level of support, education and information available to patients. Lorig et al. found that when self-management and adherence programmes are combined with regular treatment and disease-specific education, significant improvements in health-promoting behaviours, cognitive symptom management, communication and disability management have been observed. These positive changes can result in reduced hospitalisation rates as well as a decrease in the number of days

Fig. 1. Percentage of people who own a mobile phone by Living Standard Measurement (SAARF AMPS 2008).

Fig. 2. Use of mobile phone (excluding voice calls) recorded over the past week among owners and users of mobile phones (SAARF AMPS 2008).
spent in hospital and outpatient visits. In addition, data suggest a cost-to-savings ratio of approximately 1:10 in some cases, and these results persisted over 3 years. The following services will be reviewed, and future work and research will need to assess whether they are cost effective and reduce expensive events such as hospitalisation.

- Appointment reminders
- Self-assessment tests
- Social support networks
- Daily diary
- Surveys and follow-up
- Information service.

**APPOINTMENT REMINDERS**

An automated SMS service that reminds people of their next appointment can help reduce loss of follow-up and adherence. Pinsker et al. examined an outpatient service and found that the most important step a provider could take to improve adherence with follow-up was to schedule appointments before the patients were sent home. Patients with scheduled appointments were almost 10 times more likely than others to receive follow-up.

A South African example of using SMS for appointment reminders is the txtalert service. txtalert was created by the Praekelt Foundation and is used in Right to Care’s Themba Lethu Clinic. Preliminary results show that the appointment reminders have reduced the ‘lost to follow-up’ rate to less than 4% in a clinic managing 7,000 patients. In addition to the appointment reminders, patients are able to make use of the system, at no cost to them, to change their appointment date.

**SELF-ASSESSMENT TESTS**

Research shows that if people understand that they are in a high-risk category for a chronic disease they are more likely to take action. An example is SexInfoSF (Fig. 4), based in San Francisco, which used social marketing to advertise an SMS-based risk assessment for sexually transmitted infections.

However, care must be taken to communicate with people at the correct level. ‘Don’t appear so scholarly. Humanise your talk, and speak to be understood’ (Molière). Use of the service spiked with every press and marketing drive. At first no users went past the first menu. In response to this challenge, SexInfoSF changed the language of the messages:

- **Old:** Reply with code 4 answers. ‘A1’ if ur condom broke
- **New:** Ttx 1 if ur condom broke

- **Old:** A1: U may b at risk 4 STDs+HIV women can also b pregnant SouthEast Keith@Armstrong 671-7000
- **New:** 1: U may be at risk 4 STDs + pregnancy. S.E. Clinic, Keith at Armstrong St, 41-671-7000

After the ‘language’ within the messages was changed, all users continued through the menu. However, once the marketing drives stopped, use of the service stopped. Sexual health was not compelling ‘enuf’ to create a viral spread of the service. Services need to be in touch with the community they serve in order to create services that are spread via social networks and recommendations from friends.

SOCIAL SUPPORT

For the effective provision of care for chronic conditions, it is necessary to activate the patient and the community which supports him or her.8 Research shows that this can be particularly effective in programmes to encourage smoking cessation, weight control or exercise, where there is substantial evidence that peer support among patients can improve adherence to therapy9-16 while reducing the amount of time devoted by health professionals to the care of patients with chronic conditions.17-19

An example from Mexico is Project Zumbido (zumbido is Spanish for ‘buzz’) (Fig. 5).

A pilot project in Mexico, run by a UK-based consultancy company called SHM, provided 40 participants in an ARV clinic with mobile phones and unlimited text messages. The project used a UK-based group messaging software called ZygoHUBS. When a user sends an SMS to a pre-arranged number the message is then received by all the participants. The aim was to record the usage patterns and whether the system helped to increase the level of social support experienced by participants. By the end of the 3-month trial period, 25 000 text messages had been sent between the 40 people participating in the project. In a follow-up survey participants reported feeling less isolated, having better support networks, and having improved relationships with their families.20

The organisers’ fear that the network would be used to send jokes was unfounded. Instead, the ‘participants began to develop meaningful relationships with each other, reaching out from behind the barriers that separate people living with HIV/AIDS from the rest of society.21 Two anecdotal stories illustrate the social support experienced by participants. One woman experienced headaches that she attributed to side-effects of the medication. She did not want to see a doctor and admit that she was not taking the medication. The other participants in her ‘mobile phone support group’ encouraged and advised her to go to see her doctor. After doing so she thanked her fellow participants by sending an SMS to the group. Another participant sent an SMS to the group regarding the long-term cancerous side-effects of a drug called nelfinavir. In response to this SMS a participant living in a rural area went back to his health facility and asked for his medication to be changed.

This expensive project was unable to continue beyond 3 months because of the costs involved in making the service available to the 40 participants. However, the Zumbido project has certainly shown the potential for a mobile phone support network to touch the lives of patients living with a chronic condition.

DAILY DIARY

Mobile phones can be used to record entries in a ‘daily diary’. Diary entries could be sent via SMS or via an application that is custom made for mobile phones. Diary entries, or active requests, via SMS have worked well in motivated and self-efficacious patients because mobile phones are a part of people’s everyday lives.22 A custom-made application would require training for both the patient and the health care provider to ensure uptake and use of the system. This system would be of use in a clinical trial where daily responses from participants can be necessary for monitoring purposes.

Treatment diaries are subject to social desirability bias, with highly motivated people reporting more frequently than less motivated people (Delany-Moretwe S, et al., ‘Motivation for participation and potential adherence issues using herpes simplex virus type 2 (HSV-2), suppressive therapy for HIV preventing among South African women: lessons for future trials’ – unpublished data). A mobile phone-based diary that is connected to an online web-based service would allow a health provider instantly to view which clients are creating daily entries. This would act as a screening device, by revealing who are the motivated patients and allowing for more time and effort to be spent on the less motivated patients.

Fig. 5. An enthusiastic Mexican and a picture from one of Project Zumbido’s workshops.
Mobile phones provide a paperless system for collecting data. These data can be sent to a server, allowing a coordinator to view the results as they come in real time. A South African example of this service is Cell-Life’s Aftercare (Fig. 6).

Cell-Life’s Aftercare service is used by trained ‘therapeutic counsellors’. These counsellors are allocated 15 - 20 patients each and follow up the patients at their homes. During the home visits the counsellors record information regarding adherence, appointment times and side-effects on the Aftercare mobile phone application. The information is logged instantaneously to a central database that can be viewed online by a central operator. This system reduces paperwork, can be used on a large scale in remote areas, and owing to the direct data entry real-time monitoring has the potential for mistakes to be corrected immediately.23

Well-timed provision of information can improve patients’ understanding of treatment and adherence. Patients may become frustrated if their preferences in treatment-related decisions are not elicited and taken into account. Examples from past research show that patients who felt less empowered in relation to treatment decisions had more negative attitudes towards prescribed antiretroviral therapy and reported lower rates of adherence.21 If a patient lacks information about the prescribed daily dosage or has misconceptions about the disease, treatments or side-effects, then adherence decreases.23

Cell-Life, in Cape Town, is developing a mobile phone-based information service for people living with or concerned about HIV. Cell-Life aims to make this service free to the end user and will provide information through the use of different means such as games, chat systems (e.g., MXIT) and voice messages. Research will be conducted to assess the effect of the information service.24

Information combined with a call to action can make use of the available advertising space on ‘please call me’ messages – for example, the ‘please call me’ advertising space has been used to advertise the AIDS helpline number. During a 20-day campaign approximately 20 million ‘please call me’ messages with the AIDS helpline number were sent and received. At the start of the campaign, Lifeline was receiving approximately 45 000 calls per month. During the campaign, call volumes increased by a massive 350% and the call centre had to work hard to take an additional 1 500 calls a day.25

CONCLUSION

Mobile phones can be used to improve delivery of health services, provide access to relevant information and increase social support, and as tools for research, monitoring and evaluation. The technology is evolving rapidly and in a few months’ time this article will be out of date. New technologies will have to prove that they are cost effective to gain traction among health managers and health professionals. The use of mobile phones in the health industry will undoubtedly increase over the next year and it is certain that they will be used as an additional tool to improve the level of health care in South Africa.

The technology is simple, but the application of mobile technology is complex. Challenges within the health setting include ethical issues such as protecting privacy, the variety of official and unofficial text (txt) languages that are being used, and the variable amount of disposable income that is available in different sectors of the South African population. Social science research, or a great deal of trial and error, is required to help guide the creation of health-related mobile phone applications that fit seamlessly and economically into people's lives.

Mobile phones are not a perfect solution. Phones can be stolen, people can change numbers, and there are times and places where the signal does not operate perfectly. This means that despite all the benefits that mobile phones offer there are still going to be some patients who slip through the net and are lost to follow up.

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South Africa has the fourth highest burden of tuberculosis (TB) worldwide after China, India and Indonesia and has the highest TB notification rate of any country. The World Health Organization (WHO) estimated that in 2006 South Africa had 303,114 incident TB cases; of these patients, 32% were tested for HIV and 53% were found to be HIV infected.\(^1\) HIV testing of TB cases has been encouraged by the WHO and testing has resulted in identification of increasing numbers of HIV-infected individuals in the TB control programme. The success of this policy has been demonstrated in the Cape Town Gugulethu antiretroviral clinic, where referrals directly from the local TB clinics have increased from 15% to 30% within the past 2 years. The national TB control programme has therefore become an increasingly important pathway to HIV care and access to highly active antiretroviral therapy (HAART). An additional 15 - 20% of patients in the Gugulethu programme have a diagnosis of TB made during the HAART screening period, further increasing the number of individuals on TB medication who require HAART. Mortality after referral is very high. The HIV/TB case mortality has been reported to be as high as 16 - 35%\(^2\) prior to the introduction of HAART, with both HIV and TB contributing to this mortality. Optimal timing of HAART is currently unknown and there is an urgent need for development of evidence-based protocols for HAART initiation and immune reconstitution disease (IRD) management.

Tuberculous meningitis occurring in HIV-infected individuals (HIV/TBM) exemplifies the dilemmas facing clinicians when addressing potentially preventable mortality. HIV/TBM has a devastating clinical impact with a median time from onset of symptoms to presentation of 10 days, 67% mortality and a median time to death of 20 days.\(^3\) Expert opinion on when to start HAART in HIV-infected patients with TB meningitis varied between 2 weeks and 12 months after starting TB medications.\(^4\) This uncertainty of expert opinion reflects the present lack of randomised clinical trial data with which to inform clinical management. A clinical trial specifically addressing immediate initiation versus deferring HAART (zidovudine/lamivudine/efavirenz) for 8 weeks has been conducted at two hospital sites in Ho Chi Minh city, Vietnam. Results of this study should become available in late 2008 or early 2009.\(^5\) A study demonstrating proof of the concept that earlier initiation of antiretroviral therapy may impact on mortality of HIV patients with active opportunistic infections (OIs) was recently presented.\(^6\) The AIDS Clinical Trials Group study 5164 (ACTG 5164) was a randomised strategy trial of immediate versus delayed ART in the setting of acute OI. At the time of inclusion study subjects had pneumocystis pneumonia (63%), cryptococcal meningitis (13%), other acute pneumonic illnesses (10%) or multiple opportunistic infections (30%). Patients were randomised to immediate or delayed initiation of HAART, a median of 12 days or 45 days after starting OI treatment, respectively. After 48 weeks, deaths in the early treatment group were significantly lower with no difference in drug toxicities, adherence or hospitalisation. Somewhat counter-intuitively, IRD was also less frequent in the earlier treatment group. The conclusion from this study was that in the absence of contraindications very early use of HAART should be considered in patients with acute OIs. However, it should be noted that TB cases were not included in this study population.

CONSIDERATIONS DETERMINING EARLIER VERSUS LATER INITIATION OF HAART

The decision when to initiate HAART after TB treatment is complex, involving a number of variables including treatment tolerance, drug co-toxicities, pharmacokinetic drug interactions and impact of polypharmacy on adherence (Fig. 1). However, of over-riding importance is the mortality associated with delays in ART initiation versus mortality associated with IRD when HAART is initiated early. The frequency of IRD in cohort studies describing co-infected patients varies markedly between 8% and 43%.\(^7,8\) The mean interval to IRD after HAART initiation also varies widely (1 - 180 days) with most cases occurring within the first 28 days.\(^7\) However, cross-cohort comparisons are complicated by differing mortality in cohorts from high- and low-resourced settings and...
differing incidences of TB-associated IRD in TB patients starting HAART in different settings. Furthermore, while variable rates of IRD may represent differences between cohorts, analysis is complicated by variable ascertainment and lack of a standardised IRD definition. A consensus document with proposed definitions of IRD for use in resource-constrained settings may help address the problem of differing case definitions. IRD is characterised by worsening of systemic symptoms, transient enlargement of pre-existing lesions, onset of new lesions including lymphadenopathy, and worsening of radiographic changes. Life-threatening conditions are rare but include tracheal and bronchial obstruction, pulmonary adult respiratory distress syndrome (ARDS), central nervous system tuberculomas and cerebral oedema. The management of life-threatening IRD includes use of high-dose steroid therapy and may necessitate interruption of HAART, although there are no randomised controlled studies to inform policy. The precise pathological processes responsible for IRD are not clearly defined, but the condition is associated with an expansion of CD4 cells in the peripheral blood and increased macrophage activity. The risk factors for development of IRD are predominantly a low CD4 cell count and a short interval between starting TB therapy and HAART initiation. In a prospective Cape Town cohort, IRD occurred in 100% and 70% of patients commencing HAART within 30 days with CD4 counts of <50 cells/μl and 50 - 100 cells/μl respectively (Fig. 3). Extrapulmonary TB and black ethnic group have been identified as additional risk factors for IRD. Severe TB-associated IRD therefore tends to develop in those patients who have a high mortality risk, manifested by low CD4 cell counts and a high mycobacterial burden associated with disseminated TB. Several studies reporting considerable morbidity associated with IRD have not shown an excess mortality. Similar findings were also reported in a South African cohort where 10.5% who developed TB-IRD died; however, 9.9% of TB patients who did not develop IRD also died. Development of IRD and IRD-associated mortality in these studies was therefore not associated with significant excess overall mortality.

Variations in IRD frequency and associated mortality indicate that the optimal timing of ART initiation may differ between settings. In lower income countries, the risk of mortality associated with delays in ART initiation is likely to outweigh the excess mortality of TB-associated IRD. The optimal timing of ART initiation may therefore be earlier in the course of TB treatment for patients in resource-limited settings compared with those in high-income settings. Current guidelines for the timing of HAART in patients with TB are shown in Table I. All these guidelines reflect an increased urgency to commence HAART at lower CD4 cell counts with variable timing recommendations due to a lack of data from randomised controlled trials. This lack of informative data is clearly reflected in the recommendations of the International AIDS Society (IAS), USA. Several guidelines focus on 8 weeks as a key time point in TB therapy when simplification of TB medications occurs. In South Africa schedule 1 TB therapy consists of an intensive four-
drug therapy (isoniazid, rifampicin, pyrazinamide and ethambutol) which is reduced to two-drug maintenance (RIF/INH) after 8 weeks. The South African TB control programme promotes use of fixed-dose combination tablets which results in identical pill burdens before and after the 8-week treatment time point. Rifampicin, the anti-TB agent with the greatest potential for drug-drug interactions with non-nucleoside and protease inhibitor antiretrovirals, is continued throughout the whole 6 months of treatment. Similarly isoniazid, with a potential for peripheral neuropathy co-toxicity with stavudine, is also continued throughout TB therapy. The main co-toxicity shared between TB and HAART is hepatotoxicity, and some staggering of initiation of the two treatment regimens may simplify clinical management of drug-induced hepatitis. Although pyrazinamide, which is routinely discontinued after 8 weeks of TB treatment, may contribute somewhat to hepatic co-toxicity, it is unproven whether the optimal deferring time period is 8 weeks.

### STUDY DATA ADDRESSING WHEN TO START HAART

Randomised controlled trials addressing the optimal timing of ART initiation in patients with TB are awaited, but meanwhile data from observational cohorts and modelling studies may help inform policy. Cohort studies have reported a markedly variable impact of HAART on TB mortality. Three cohort studies describing outcomes in patients starting HAART at different time points after TB therapy reported at the International AIDS Society 2008 Conference meeting in August 2008 highlight the difficulties in interpreting cohort data. A Brazilian clinic-based cohort study of 662 patients found no significant difference in survival between patients starting HAART in the first 2 months, 2 - 6 months or more than 6 months after commencement of TB treatment. In contrast, an Iranian study of 69 hospitalised patients showed significant increases in TB cure rate and survival in patients who started HAART within 2 weeks compared with 8 weeks of TB treatment. A third study, from Argentina, showed similar differences in TB cure rate and survival with early initiation of HAART. However, this last study also reported significant differences in baseline characteristics between the groups, demonstrating that cohort studies may be subject to considerable selection bias. A South African cohort study of the International Epidemiological Databases to Evaluate AIDS Group (IeDEA) retrospective analysis of 4,000 HIV/TB patients from multiple sites in the Free State and Cape Town will be completed and is planned for reporting during 2009.

### TABLE I. CURRENT INTERNATIONAL AND SOUTH AFRICAN GUIDELINES FOR THE TIMING OF INITIATION OF HAART IN HIV-INFECTED PATIENTS ON TB THERAPY

<table>
<thead>
<tr>
<th>Year</th>
<th>Organisation</th>
<th>CD4 count</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>2003</td>
<td>American Thoracic Society*</td>
<td>CD4 &lt;350</td>
<td>Individualise between 4 and 8 wks</td>
</tr>
<tr>
<td></td>
<td>CD4 &gt;350</td>
<td></td>
<td>Defer HAART</td>
</tr>
<tr>
<td>2004</td>
<td>MMWR† (Pediatrics)</td>
<td>CD4 &lt;200</td>
<td>Defer 4 - 8 wks</td>
</tr>
<tr>
<td></td>
<td>CD4 200 - 350</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>CD4 &gt;350</td>
<td></td>
<td>Defer HAART</td>
</tr>
<tr>
<td>2004</td>
<td>WHO &quot;Scaling up ART in resource-limited settings&quot;‡</td>
<td>CD4 &lt;50</td>
<td>2 wks - 8 wks</td>
</tr>
<tr>
<td></td>
<td>CD4 &lt;200</td>
<td></td>
<td>Start at 2mo.</td>
</tr>
<tr>
<td></td>
<td>CD4 &gt;200</td>
<td></td>
<td>6 mo.</td>
</tr>
<tr>
<td>2006</td>
<td>IAS/USA panel¶</td>
<td>CD4 &lt;100</td>
<td>Individualise as there are no RCTs</td>
</tr>
<tr>
<td>2008</td>
<td>DHHS: Guidelines**</td>
<td>CD4 100 - 200</td>
<td>2 wks</td>
</tr>
<tr>
<td></td>
<td>CD4 200 - 350</td>
<td></td>
<td>8 wks</td>
</tr>
<tr>
<td></td>
<td>CD4 &gt;350</td>
<td></td>
<td>8 - 24 wks or defer</td>
</tr>
</tbody>
</table>

the Vietnamese TB meningitis study is expected to be able to report outcomes in the near future (Table II). The Cambodian Early versus Late Introduction of Antiretrovirals (CAMELIA), a large randomised open-labelled study conducted in five sites in Cambodia, should be the first of these studies to report outcomes, some time during 2009 or 2010.29 Unexpectedly, preliminary data from the Starting Antiretroviral therapy in three Time Points in Tuberculosis (SAPIT) study conducted in KwaZulu-Natal became available in September 2008 owing to the data safety and monitoring board (DSMB) discontinuing the third randomisation arm of the study because of a 55% increased mortality in subjects deferring HAART for 6 - 8 months.31

**DISCUSSION**

Determination of the optimal timing of initiation of ART in patients with TB is urgently needed in South Africa, where HIV/TB is extremely common and availability of HAART is rapidly expanding. HIV/TB case fatality rates are high and the optimal deferral time will therefore be determined predominantly by mortality rather than morbidity. Unfortunately the results of several randomised controlled trials addressing when to start HAART in TB, with a primary endpoint of survival, will not be available until 2009/2010. Meanwhile, preliminary data from the SAPIT study indicate that deferring treatment for 6 months is associated with significantly increased mortality.31 The Vietnamese study results of immediate initiation of HAART in TBM should become available in the next few months.5 The results of this study may not necessarily be generalisable to other forms of TB; however, any significant mortality benefit of immediate initiation of HAART will bolster support for earlier treatment in other severe forms of TB.

The present status of information concerning the most important factors that may impact on the optimal timing of HAART in TB are shown in Fig. 4. Reduction of ongoing HIV-related mortality by HAART is counterbalanced by TB/IRD-associated mortality and a clinical need to stagger the initiation of both treatments for ease of clinical management of co-toxicity. Those at highest risk of HIV progression also have the highest risk of co-toxicity and IRD. The ACTG 5164 study has demonstrated improved survival with very early initiation of HAART in patients co-infected with acute OIs.6 Treatment of TB requires prolonged treatment and is complicated by frequent occurrence of IRD. However, published reports indicate that while TB/IRD is a common cause of morbidity it is a less frequent cause of death.

Much interest has rightly focused on the optimal timing of HAART in relation to TB treatment. In low-income settings TB in HIV-infected patients is often only

**TABLE II. ONGOING TRIALS OF HAART IN HIV-INFECTED INDIVIDUALS ON TB THERAPY**

<table>
<thead>
<tr>
<th>Trial (sponsor)</th>
<th>CD4 (µl)</th>
<th>Time (design)</th>
<th>Study design</th>
<th>End-points</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAMELIA (NIH/ANRS)</td>
<td>&lt;200</td>
<td>12 mo. (ROL*)</td>
<td>2 wks v. 8 wks after TB initiation (N=660, accruing results 2009/10)</td>
<td>Survival</td>
</tr>
<tr>
<td>ACTG S221 (NIAID)</td>
<td>&lt;200</td>
<td>12 mo. (ROL*)</td>
<td>2 wks v. 12 wks after TB initiation (N=200 of 800 accrued)</td>
<td>AIDS-free survival</td>
</tr>
<tr>
<td>SAPIT (NIAID)</td>
<td>&gt;50</td>
<td>18 mo. (ROL*)</td>
<td>&lt;2 mo. v.&gt;2 mo. v. post 6 - 8 mo. TB Rx (N=645, DSMB stopped 3rd arm)</td>
<td>Survival</td>
</tr>
<tr>
<td>TB-HAART (WHO/TDR)</td>
<td>&gt;200</td>
<td>6 mo. (RPC†)</td>
<td>HAART at 2 wks v. placebo at 2 wks (N=1 900 accruing results 2011)</td>
<td>Survival, TB failure</td>
</tr>
<tr>
<td>TB meningitis (Wellcome Trust)</td>
<td>All</td>
<td>9 mo. (RPC†)</td>
<td>Immediate v. 8 wks ART + steroids (N=247, accrued results Dec 2008)</td>
<td>Survival</td>
</tr>
</tbody>
</table>

*Randomised open-label study. †Randomised placebo-controlled study.
NIH = National Institute of Health; ANRS = Agence Nationale Recherche sur Le Sida; NIAID = National Institute of Allergy and Infectious Disease; WHO = World Health Organization; TDR = Tropical Disease Research.
diagnosed after prolonged delay, and yet the mortality associated with even short delays in accessing HAART is unacceptable high. Furthermore, the potentially more important problem of delays in the care pathway has received little attention.

While the results of randomised controlled studies addressing the timing of initiation of HAART are eagerly awaited, the results may still not be generalisable to all types of TB, HIV progression, race and health systems. In the meantime it is important to recognise that time delays between the onset of TB symptoms and starting HAART in those eligible for HAART are associated with potentially preventable HIV-related mortality and that all potential delays should be minimised.

REFERENCES


The most effective way to combat paediatric HIV infection is through good management of maternal health and prevention of mother-to-child transmission (PMTCT). However, by the end of 2007, of an estimated 33.2 million people living with HIV, 2.1 million were children. Of these 90% lived in sub-Saharan Africa and 420 000 were newly infected in that year.1

Although in recent years the number of children treated with antiretroviral therapy (ART) has increased from about 75 000 in 2005 to almost 200 000 in 2007, many children living with HIV are not receiving treatment. Without it approximately 35% will die before their first birthday and 53% by the time they reach the age of 2 years.2 By age 5 years it is estimated that 62 - 89% of children will have died.3,4

Emerging data from sub-Saharan Africa show that most children starting ART are doing so at older ages, usually 5 years or more, that most start at a late stage of the disease, and that mortality in the first few months of treatment remains high.5,6

A recent study shows that starting treatment in early infancy can be lifesaving, and this has informed revisions in World Health Organization (WHO) guidelines7,8 (see WHO ‘Dear Health Care Provider’ letter, Fig. 1). At present the majority of children who could benefit from these recommendations are not being diagnosed or treated.

A literature review of 30 paediatric studies or treatment programmes found that children receiving ART ranged from infants aged 2 months to adolescents aged 15 years.5 Of 26 studies that reported age at ART initiation, 19 (73%) showed a mean or median age at start of treatment of >5 years. Only two studies reported a median age at start of treatment of <2 years.

The majority of children assessed in this review had severe immunosuppression at initiation of ART. The proportion of children with a CD4 percentage <15% ranged from 56% to 96%.

Overall mortality during follow-up was mostly low, with a probability of survival at 1 year after initiation of ART of 84 - 97%. A study from Cote D’Ivoire reported over 3 years of follow-up, with 92 - 93% survival 6 months after initiation of ART, 91% at 12 months, 88% at 18 - 36 months and 86% at 42 months.

The majority of deaths occurred within 6 months of starting ART. The most commonly reported risk factor for death was low CD4 percentage at initiation of treatment. Age >12 - 18 months was among the other risk factors reported.

Data from the KIDS-ART-LINC Cohort Collaboration (an international epidemiological network in sub-Saharan Africa) concur with the above findings.6 They report children starting ART at an average of 4.9 years, with only 12% starting at <12 months. Seventy per cent of children starting ART had severe immunodeficiency. The 2-year risk of death on ART was 6.9% (95% confidence interval (CI) 5.9 - 8.1%), and this was independently associated with immunodeficiency, adjusted hazard ratio (AHR) 2.95 (95% CI 1.49 - 5.83) and advanced clinical disease AHR 3.65 (95% CI 1.95 - 6.83).

KIDS-ART-LINC shows an increase in mortality risk in children starting ART when severely immunodeficient compared with children who were not immunodeficient, with the probability of death at 6 months rising from 1.8% to 7.8%.9 Twelve months after starting ART the probabilities of death are 2.2% and 8.2% respectively.

Of note, where the entry point is reported, the majority of children are identified and enrolled into ART programmes through health facilities when they are treated when clinically indicated rather than as infants through PMTCT programmes.

Only two studies assessed in the literature review report how children were referred for ART.1 In a Kenyan
Programme data from Malawi show that only 1% of children starting treatment were identified through PMTCT programmes. Programme data from Malawi also show that only 1% of children starting treatment were identified through PMTCT programmes.

In Côte d’Ivoire, the paediatric department or other health care settings referred 64% of children, 24% were referred through the programme living with HIV/AIDS network and 12% through the PMTCT programmes. Programme data from Malawi show that only 1% of children starting treatment were identified through PMTCT programmes.

Fig. 1. WHO ‘Dear Health Care Provider’ letter.
PMTCT follow-up, with the vast majority (80%) enrolled for ART through hospital wards.\textsuperscript{10}

The WHO reports that only 8% of infants born to pregnant women with HIV in 2007 were tested for HIV before they were 2 months old.\textsuperscript{1}

**EVIDENCE FOR EARLY TREATMENT FROM THE CHER STUDY**

The Children with HIV Early Antiretroviral Therapy (CHER) study, conducted in South Africa, is looking at whether early limited ART until a child’s first or second birthday would have long-term benefit by delaying disease progression and/or delaying the time when long-term continuous ART needs to be initiated.\textsuperscript{7} In this study 377 young infants aged 6 - 12 weeks with a CD4 percentage >25% were randomised to three arms:

- **Arm 1**: Deferred treatment – ART when the CD4 percentage declined to <20% (25% if <1 year; based on WHO guidelines).
- **Arm 2**: Short course (to first birthday) – ART with planned interruption at 1 year.
- **Arm 3**: Long course (to second birthday) – ART with planned interruption at 2 years.

ART was started or restarted in all arms when the CD4 percentage fell to <20% (25% in infants from August 2006) or the CD4 count fell to <1 000 cells/μl if age <12 months, or if indicated by a clinical event.

All infants were drug-naïve except for PMTCT prophylaxis (either nevirapine (NVP) single dose to mother and baby - 68% arm 1; 64.3% arms 2/3, or NVP plus short-course zidovudine (AZT) - 21% arm 1; 20.2% arms 2/3). The infants’ ART regimen was AZT + lamivudine (3TC) + lopinavir/ritonavir (LPV/r).

Following a data safety monitoring board (DSMB) review on 20 June 2007, after the trial was fully recruited and at a median follow-up of 32 (range 20 - 48) weeks, the DSMB recommended modification to the study and the release of the results of arm 1 vs. arms 2/3 combined. They recommended that infants in arm 1 should be recalled urgently and assessed for ART initiation and that the trial follow-up should continue.

At the time of the review, 10 (4%) infants in arms 2/3 and 4 (3.2%) in arm 1 were lost to follow-up. By the end of April 2007, 61 (59%) infants had initiated ART in arm 1. A total of 30 infants had died: 10 (4%) in arms 2/3 and 20 (16%) in arm 1 (hazard ratio (HR) 0.24 (95% CI 0.11 – 0.52); \(p=0.0002\)).

Of the infants who died, 12 died at home from unknown causes. Causes of death in the 18 infants who died in hospital were gastroenteritis (4, arm 1; 4 arms 2/3), sepsis/pneumonia (5 arm 1; 0 arms 2/3), Pneumocystis jiroveci pneumonia/cytomegalovirus infection (3 arm 1; 0 arms 2/3), sudden infant death syndrome (0 arm 1; 1 arms 2/3), liver failure (0 arm 1, 1 arms 2/3).

The investigators noted that the deaths in this study were not always from AIDS-defining causes and were often sudden.

The CHER study found that starting ART before 12 weeks of age reduced early mortality by a highly significant 75% compared with starting at CD4 percentages <25% or guided by clinical symptoms.

**NEW WHO RECOMMENDATIONS**

On 13 June 2008, following a technical review of these data and another small study conducted in South Africa that supports the CHER findings, the WHO revised their guidelines to recommend universal treatment of all HIV-infected infants <12 months of age.\textsuperscript{7,8,11} The WHO strongly recommends that ‘All infants under 12 months of age with confirmed HIV infection should be started on ART, irrespective of clinical or immunological stage.’

In order to benefit from early treatment and to reduce their risk of disease and death, infants will need to be tested at the earliest opportunity.

For diagnosing infants the WHO strongly recommends that:

- Infants known to be HIV exposed, i.e. born to mothers in PMTCT programmes, have a virological test (HIV nucleic acid test) at 4 - 6 weeks of age.
- Any infant presenting at a health facility with signs or symptoms that may be an indication for HIV, should initially be tested using an HIV antibody test with a positive test confirmed by virological testing if possible.
- All infants should have their HIV status established at their first contact with the health system, preferably before 6 weeks of age (in most cases this will be established by asking the mother and checking her history of HIV testing).
- They also conditionally recommend that infants <6 weeks of age in settings of high antenatal HIV prevalence (i.e. >1%) should be offered maternal or infant HIV antibody testing.

The WHO recommends that infants are diagnosed using virological tests (HIV DNA polymerase chain reaction (PCR), HIV RNA PCR or bDNa or NASBA, or ultrasensitive p24 antigen). The HIV DNA PCR is the only test that can be performed using dried blood spot samples and is the most useful for early diagnosis in PMTCT follow-up.

They also recommend that testing is performed around 4 - 6 weeks for PMTCT follow-up, and whenever an infant...
is sick or HIV is suspected in those known to be exposed. Testing at 4 weeks instead of at 6 weeks provides an additional 2 weeks to start treatment at a time when the infant is very vulnerable.

If virological testing is not available, the WHO recommends presumptive diagnosis in accordance with nationally defined algorithms. Based on data from the CHER study, they are refining an algorithm based on symptoms and signs of HIV at 6 weeks of age. Although lacking sensitivity, suggestive signs include oral thrush, hepatomegaly, splenomegaly, lymphadenopathy, diapheratitis, and clinical gastro-oesophageal disease (cough and/or vomiting during feeds).

### STARTING TREATMENT

The guidelines recommend ART regimens as follows:

- No maternal or infant antiretroviral exposure; exposure to antiretrovirals other than non-nucleoside reverse inhibitors; unknown exposure - NVP-containing triple ART.
- Maternal or infant single-dose NVP or maternal NNRTI-containing ART - PI-containing triple ART (usually LPV/r).

Paediatric formulations for children too young to swallow tablets have traditionally been liquids or syrups. These formulations are expensive and not easy to store or transport. Cost and logistical issues have prohibited their widespread use. This example illustrates the challenge faced by the caregiver: 'A 10 kg child being treated with standard doses of stavudine, lamivudine, and nevirapine, for whom a 3-month supply of drugs is dispensed at a clinic visit, would require 18 bottles of liquid weighing almost half as much as the child (4.3 kg). For a rural family who may have walked a long distance to reach the clinical centre, this is a significant issue.'

More recently manufacturers have developed more convenient crushable mini-pills or dispersable formulations and fixed-dose combinations, which can be used by very young children. Many programmes are now using these formulations and the WHO recommends dosing according to its simplified weight band tables (see Fig. 2).

The WHO have also identified data and formulations that need to be provided as a matter of urgency in order to support the revised recommendations:

- Additional data on dosing of efavirenz (EFV) for young children and infants
- Dosing for LPV/r for the group under 6 months and 5 kg based on a target dose of 300 mg/m²
- LPV/r sprinkles (50/12.5 mg)
- Atazanavir/ritonavir (ATV/r) (heat stable)
- Ritonavir (RTV) (solid, heat-stable forms).

### COMMENT

These recommendations from the WHO are welcome, and having a single 'one size fits all' policy that can be implemented without waiting for CD4 results will make

![Fig. 2. Summary of simplified dosage of antiretrovirals for infants and children.](starting infants.indd 31)
starting paediatric ART more feasible. Nevertheless, implementing universal treatment for HIV-positive infants will be no small matter. Data show that currently only a few young infants are being identified and enrolled in treatment programmes in sub-Saharan Africa. The majority of children who receive ART are being diagnosed and start at about 5 years old, by which time many who needed it will have died.

The CHER investigators wrote that their results ‘... support the need for enhanced PMTCT programmes, early infant diagnosis and effective transition to care’.

Firstly, then, the focus on PMTCT deserves emphasis. Identifying and treating an HIV-positive pregnant woman who meets the eligibility criteria for ART or ensuring that a healthier HIV-positive woman receives an effective prophylaxis regimen (some would say ART for all) – and in turn avoiding the majority of paediatric infections – surely must be a massive priority. Taking appropriate care of an easier-to-manage adult patient can avoid an additional, more complicated paediatric case, and where this has not been possible, the goal of universal ART for HIV-positive infants will be far easier to achieve with lower mother-to-child transmission rates.

Secondly, running DNA PCR tests in order to diagnose infants early enough to benefit from these recommendations is not going to be feasible in many places. Low-cost, simple diagnostic assays are urgently needed. In the meantime, improved clinical and laboratory-based algorithms are expected to refine the specificity of presumptive diagnosis. Clear recommendations are needed for repeat testing in breastfeeding populations.

Thirdly, better links between PMTCT and treatment programmes for those children who are infected are important and will reduce delays in starting infants on ART.

Finally, we need good data to give guidance as to whether, once started, ART can be safely stopped in children after early initiation, and if it can, when the best time will be to resume therapy.

The author would like to thank Siobhan Crowley, Mark Cotton and Di Gibb for discussion of these data and recommendations.

REFERENCES

Forty per cent of HIV-infected children die before they reach their first year of life, mainly in the first 6 months. Data from the Children with HIV Early Antiretroviral Therapy (CHER) study indicate that even when infants appear well and their CD4 counts are >25% there is a 75% increased risk of mortality when antiretroviral therapy (ART) is deferred until threshold CD4 depletion occurs or clinical criteria are met. Even after starting ART, young infants have excess mortality within the first year of life. Every effort should therefore be made to identify HIV-infected infants as early as possible so that ART can be initiated without delay.

**EARLY DIAGNOSIS**

Owing to the high prevalence of HIV in southern Africa, the HIV status of all infants (and their mothers) accessing any health care facility (including consulting rooms of family practitioners, immunisation clinics, hospitals, etc.) for any reason should be determined.

- **Mother known to be HIV positive, infant’s status unknown** – DNA PCR testing for infant as early as possible.
- **Mother’s HIV status unknown** – rapid HIV test for mother or infant if mother unavailable, followed by a DNA PCR for infant if either rapid test is positive.
- **Mother HIV negative during pregnancy** – offer repeat rapid HIV testing for mother and/or infant. If either is positive, then DNA PCR testing for infant.

All HIV-positive mothers should have a CD4 count done and be referred urgently for care if the CD4 count is <350 cells/μl. (The Southern African HIV Clinicians Society recommends initiation of ART in all pregnant HIV-positive women where resources are available.)

Once an HIV diagnosis is made in the infant, **ALL HIV-infected infants should urgently be referred to an ART treatment site.**

Start all HIV-exposed infants on co-trimoxazole from at least 4 - 6 weeks.

Immunisation should continue as per the Expanded Programme on Immunization.

When infants are diagnosed as HIV positive (i.e. by polymerase chain reaction (PCR)), mothers should be encouraged to continue or re-initiate breast-feeding.

**ANTIRETROVIRAL THERAPY**

According to recently updated recommendations from the World Health Organization (WHO) in June 2008, all HIV-infected infants <12 months of age must be fast-tracked to receive ART.

The interval between identification, adherence counselling and commencing ART should be as short as possible (1 – 2 weeks) as infants deteriorate rapidly. Adherence counselling should continue after commencement of treatment.

ART can be initiated after the first positive PCR, while awaiting confirmatory studies such as plasma HIV RNA (usually done at baseline before starting ART).

Infants diagnosed with HIV infection in hospital should be prepared and started on ART before discharge whenever possible (i.e. in most cases).

All infants in South Africa should be started on a combination of:
- Stavudine 1 mg/kg/dose bd (abacavir at 8 mg/kg/dose bd preferred)
- Lamivudine 4 mg/kg/dose bd
- Lopinavir/ritonavir (LPV/r) 300 mg/m²/dose bd (the WHO recommends LPV/r when NVP is used for prevention of mother-to-child transmission (PMTCT)).

Even when infants start ART early they remain at increased risk of illness and death, particularly in the first few months. All infants under 12 months old, even after starting on ART, should be assessed monthly until their first birthday.

REFERENCES
CHANGES IN BODY COMPOSITION AND OTHER ANTHROPOMETRIC MEASURES OF FEMALE SUBJECTS ON HIGHLY ACTIVE ANTIRETROVIRAL THERAPY (HAART): A PILOT STUDY IN KWAZULU-NATAL, SOUTH AFRICA

Background and objectives. An understanding of the effect of highly active antiretroviral therapy (HAART) on various aspects of health, including nutritional status, is needed to ensure that population-specific guidelines can be developed for South Africa. This study aimed to investigate the changes in body composition and other anthropometric measures that occur in HIV-infected women after the initiation of HAART and to explore the relationship between these measures and CD4 lymphocyte count.

Design and setting. A longitudinal study was carried out at the Umkhumbane Community Health Centre, KwaZulu-Natal.

Subjects. 30 HIV-infected adult women who started HAART between March 2007 and October 2007.

Methods. Anthropometric measurements and bioelectrical impedance analysis were performed at baseline and 24 weeks after commencing HAART. CD4 lymphocyte counts were done at baseline and at the 24-week visit.

Results. There was a statistically significant increase in all anthropometric measures except waist-hip ratio and lean body mass. The mean weight change (± standard deviation) was 3.4±5.8 kg (p=0.006). Mean body mass index (BMI) (kg/m²) increased from 25.6±5.7 to 27.3±6.6 (p=0.007). Seventy per cent of subjects gained weight, 18.5% had a stable weight and 11.1% lost weight. Subjects with lower CD4 lymphocyte counts experienced greater increases in weight, BMI, fat mass and body fat percentage. No significant association was found between anthropometric changes and change in CD4 count between baseline and the 24-week visit.

Conclusions. The findings demonstrate the value of including circumference measurements and body composition techniques as part of nutritional status assessment. Research is needed to determine the best methods of bringing about favourable anthropometric changes to enhance the health of patients on HAART.

As the patient load at antiretroviral clinics increases with the drive to meet the goals of the HIV, AIDS and STI Strategic Plan for South Africa, 2007 - 2011, there is a need to conduct research to enable the development of population-specific guidelines and policies. An understanding of the effect of highly active antiretroviral therapy (HAART) on various aspects of health of HIV-infected individuals in South Africa, including nutritional status, is needed.

Although there are data available from some African countries indicating that HAART may result in changes in body composition and other anthropometric measures, no such figures for South African adults have been published in the peer-reviewed literature.

This prospective study was therefore carried out to investigate the changes, if any, that occur in HIV-infected women receiving HAART in a primary health care set-
METHODS

STUDY POPULATION

The study sample was drawn from patients on the MTCT-Plus Programme at Umkhumbane Community Health Centre, Cato Manor, KwaZulu-Natal. The majority of the patients live in the Cato Manor urban informal settlements, where the homes consist of shacks and low-cost housing, many without running water, electricity or a water-borne sewage system. The clinic serves a predominantly Zulu population. The first 30 women, 18 years of age or older, who started HAART for the first time between March 2007 and October 2007; met the eligibility criteria; and provided written informed consent were consecutively enrolled into the study. Exclusion criteria included current pregnancy or recent pregnancy (delivery in the previous 8 weeks) and any malignant disease. Individuals were eligible to commence HAART if they had a CD4 lymphocyte count of below 200 cells/µl, World Health Organization (WHO) clinical stage 4 disease irrespective of CD4 lymphocyte count, or WHO clinical stage 3 disease with a CD4 count of 200 - 350 cells/µl.2

Ethics approval was obtained from the Committee for Human Research at Stellenbosch University and the Bioethics Committee of the Nelson R Mandela School of Medicine, University of KwaZulu-Natal.

STUDY PROCEDURES

All measurements were performed on the day HAART was commenced and then again after 24 weeks on HAART. Anthropometric measurements were performed by the principal investigator and included weight, height, mid-upper arm circumference (MUAC), waist circumference and hip circumference. Standardised techniques and the same equipment were used for all measurements. The measurements were taken in duplicate and the mean of the two measurements was used.3

Weight was measured using an electronic scale and recorded to the nearest 0.1 kg. Subjects were weighed without shoes and wearing only light clothing. Height was measured using a stadiometer (SECA 225). Subjects were measured without shoes and standing in an upright position. The head was positioned in the Frankfort horizontal plane and the subjects were asked to relax their shoulders and stand with their arms at their sides.1

MUAC was measured on the right side for all subjects. The measurement was taken at the mid-point between the top of the acromion process of the scapula and the olecranon process of the ulna and was measured with the arm hanging freely at the subject’s side.4 Waist circumference was measured with the tape measure positioned around the abdomen at the mid-point between the lowest rib and the iliac crest after the subject had gently exhaled. Hip circumference was measured as the maximal circumference over the buttocks. Circumference measurements were performed using a flexible, inelastic tape measure (SECA). Height and circumference measurements were recorded to the nearest 0.1 cm.4

The body mass index (BMI) was calculated by dividing the weight of the subject by their height squared (kg/m²) and the waist-hip ratio (WHR) was calculated by dividing the waist circumference by the hip circumference. The measurements obtained, as well as these indices, were then used to classify the individuals according to the WHO cut-off values.5 Subjects were classified into the following BMI categories: underweight (<18.5); normal weight (18.5 - 24.9); overweight (25.0 - 29.9) and obese (≥30). A WHR greater than 0.85 indicates accumulation of abdominal fat, and a waist circumference ≥80 cm and ≥88 cm identifies individuals at increased risk and substantially increased risk of cardiovascular disease, respectively.5

Bioelectrical impedance analysis (BIA) was performed using a quad-frequency analyser (Bodystat® QuadScan 4000 Hydration/Body Composition Monitoring Unit, Isle of Man, UK), which is a battery-operated unit that is connected to the body by electrodes, to allow a small electric current to pass through the body. A measurement of the impedance to the current in the body is then obtained and is used to estimate total body water (TBW) and calculate lean body mass (LBM) and body fat using regression equations. To enhance reliability, all the assessments were performed by the principal investigator and the analyser was calibrated before each analysis using the calibrator supplied by the manufacturer. Measurements were performed according to the manufacturer’s instructions (Bodystat® QuadScan 4000 User’s Guide) and using standardised procedures and electrode placements.6

It could not be assumed that the BIA equations built into the analyser by the manufacturer were suitable for use in black African HIV-infected women in South Africa, so we developed our own population-specific equation to calculate LBM as part of an ancillary study attached to the same study population. LBM was derived from the TBW, which was measured by the deuterium isotope dilution method, and impedance values were obtained using the abovementioned analyser in a sample of 50 HIV-infected women from the same study population. Stepwise multiple regression analysis was used to develop the prediction equation and the correlation coefficient was 0.873, showing a good fit between the values obtained from the equation using impedance values from the BIA and the deuterium dilution method. The subjects’ impedance values obtained from the BIA were then used in the pre-
diction equation to calculate the LBM of the subjects in the current study. Fat mass (FM) was calculated by subtracting the LBM from total body weight. Body fat percentage (BF%) was calculated by dividing fat mass by body weight and multiplying the value by 100.

Viral loads were performed by in vitro NASBA® HIV-1 assay using the Nuclisens Easy-Q-HIV-1 Viral Load Method (bioMérieux SA, Mercy L’Etoile, France), and CD4 lymphocyte counts were done by flow-cytometry using the BD Faascalibur Method (Becton Dickinson, San Jose, CA, USA). A viral load of less than 25 copies/ml was considered undetectable as this is the lower detection limit of the Nuclisens Easy-Q-HIV-1 Viral Load Assay.

The HAART regimens used by the MTCT-Plus Programme are consistent with the WHO guidelines. All subjects were prescribed the first-line HAART regimen, which is based on a combination of one non-nucleoside reverse transcriptase inhibitor (NNRTI), either nevirapine (NVP) or efavirenz (EFV), with two nucleoside analogue reverse transcriptase inhibitors (NRTIs), which consisted of lamivudine (3TC) and either stavudine (D4T) or zidovudine (AZT).

Although the national guidelines made provision for food parcels for patients on HAART, owing to provincial budgetary constraints the supply at the clinic was inconsistent and none of our patients was able to access these food parcels for any significant time period. No incentives were provided to patients to participate in the study, as all measurements were done during their routine visits.

STATISTICAL ANALYSES

Continuous variables were summarised using means and standard deviations (SDs) and were compared using paired t-tests. Categorical data were summarised using proportions and percentages. For the purpose of analysis, subjects with an undetectable viral load were assigned a viral load of 24 copies/ml or 1.4 log10 copies/ml. Subjects were also categorised according to their body weight changes between baseline and the 24-week visit as follows: weight loss, weight gain or weight stable. Correlation analysis was performed to investigate the relationship between variables and was expressed using Spearman’s correlation coefficient. A p-value of less than 0.05 was considered statistically significant. The statistical analyses were carried out by a statistician using Statistica (Version 8; StatSoft 2007, Tulsa, OK, USA).

RESULTS

BASELINE CHARACTERISTICS

A total of 30 subjects were enrolled into the study. The participants had a mean age (± SD) of 30.9±5.6 years. Table I presents the baseline characteristics of the 30 women enrolled into the study, including the baseline socio-demographic, anthropometric and laboratory parameters.

The mean weight (± SD) of the subjects at baseline was 63.7±16.0 kg [range 40.5 - 109.6 kg], the mean BMI was 25.6±5.7 [range 14.5 - 37.8] and the mean BF% was 32.2±9.7% [range 7.1 - 48.0%]. Only 2 (6.7%) of the subjects were underweight (BMI <18.5) at baseline, while 13 (43.3%) were of normal weight (BMI 18.5 - 24.9), 9 (30.0%) were overweight (BMI 25 - 29.9) and 6 (20.0%) were obese (BMI >30).

CHANGES IN ANTHROPOMETRIC MEASUREMENTS AFTER THE INITIATION OF HAART

Twenty-seven of the 30 subjects completed the 24-week follow-up period. Two subjects died and one was lost to follow-up before the 24-week visit. The mean weight, BMI, MUAC, waist and hip circumferences and WHR at baseline and 24 weeks after the initiation of HAART are set out in Table II. The values for LBM, FM and BF%, as determined by BIA, are also presented, as are the mean changes for each of the anthropometric measures.

Overall, there was a statistically significant increase in all anthropometric measures after the initiation of HAART, except for WHR and LBM (Table II). The mean weights (± SD) at baseline and after 24 weeks were 63.7±16.0 kg and 68.2±15.0 kg, respectively. This was an average weight change of 3.4±5.8 kg (p=0.006). A considerable proportion of the subjects (50%; N=15) had a BMI above the upper limit of the normal range at baseline, and this increased to 67% (N=18) by the 24-week visit, with 30% (N=8) of these subjects being obese. The mean BMI of the subjects at baseline was 25.6±5.7, and this increased to 27.3±5.6 by the 24-week visit (p=0.007).

Although the majority of the subjects gained weight (N=19; 70.4%) after 24 weeks on HAART, 3 (11.1%) lost weight and 5 (18.5%) had a body weight that remained stable. In those who gained weight the average weight gain was 5.6±5.3 kg (p=0.000) [range 1.2 - 24.7 kg]. The subjects who lost weight, lost an average of 4.6±1.6 kg (p=0.037) [range 2.9 - 6.0 kg] by the 24-week visit.

The subjects experienced a mean (± SD) increase in CD4 lymphocyte count of 120±114 cells/μl (p=0.000) and a mean decrease in viral load of log 2.7±1.2 copies/ml (p=0.000) between baseline and the 24-week follow-up visit.

Of the 19 subjects who gained weight between baseline and the 24-week visit, 68.4% (N=13) gained mostly FM and 32.6% (N=6) gained mostly LBM. Three of the 5 subjects with a stable body weight lost FM and gained LBM, while the proportions of FM and LBM remained stable in the other 2. In the 3 subjects who lost weight after
commencing HAART, the weight loss consisted mainly of LBM (4.8±3.8 kg; p=0.159).

Six subjects had evidence of disproportionate gains and losses in body circumference measurements. Three subjects experienced an increase in waist circumference and a simultaneous decrease in hip circumference, and 3 experienced an increase in waist circumference with a simultaneous decrease in hip circumference and MUAC.

**TABLE I. BASELINE CHARACTERISTICS OF THE 30 WOMEN ENROLLED INTO THE STUDY**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Subjects (N=30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>30.9±5.6</td>
</tr>
<tr>
<td>Education (yrs)</td>
<td>9±3</td>
</tr>
<tr>
<td>Employed</td>
<td>16 (53.3)</td>
</tr>
<tr>
<td>No piped water in home</td>
<td>11 (36.7)</td>
</tr>
<tr>
<td>No electricity in home</td>
<td>14 (46.7)</td>
</tr>
<tr>
<td>Previous pregnancy</td>
<td>30 (100)</td>
</tr>
<tr>
<td>No. of previous pregnancies</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>6 (20.0)</td>
</tr>
<tr>
<td>2</td>
<td>15 (50.0)</td>
</tr>
<tr>
<td>3 or more</td>
<td>9 (30.0)</td>
</tr>
<tr>
<td>Initial HAART regimen</td>
<td></td>
</tr>
<tr>
<td>AZT, 3TC, NVP</td>
<td>17 (53.3)</td>
</tr>
<tr>
<td>AZT, 3TC, EFV</td>
<td>8 (26.7)</td>
</tr>
<tr>
<td>d4T, 3TC, EFV</td>
<td>5 (16.7)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>63.7±16.0</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25.6±5.7</td>
</tr>
<tr>
<td>&lt;18.5 (underweight)</td>
<td>2 (6.7)</td>
</tr>
<tr>
<td>18.5 - 24.9 (normal weight)</td>
<td>13 (43.3)</td>
</tr>
<tr>
<td>25 - 29.9 (overweight)</td>
<td>9 (30.0)</td>
</tr>
<tr>
<td>≥30 (obese)</td>
<td>6 (20.0)</td>
</tr>
<tr>
<td>MUAC (cm)</td>
<td>28.3±5.1</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>84.5±11.6</td>
</tr>
<tr>
<td>Hip circumference (cm)</td>
<td>98.6±13.2</td>
</tr>
<tr>
<td>WHR</td>
<td>0.86±0.05</td>
</tr>
<tr>
<td>Waist circumference ≥80 cm</td>
<td>9 (30.0)</td>
</tr>
<tr>
<td>Waist circumference ≥88 cm</td>
<td>9 (30.0)</td>
</tr>
<tr>
<td>WHR &gt;0.85</td>
<td>17 (56.7)</td>
</tr>
<tr>
<td>LBM (kg)</td>
<td>41.9±5.7</td>
</tr>
<tr>
<td>FM (kg)</td>
<td>21.8±11.2</td>
</tr>
<tr>
<td>BF%</td>
<td>32.2±9.7</td>
</tr>
<tr>
<td>CD4 cell count (cells/μl)</td>
<td>164±69</td>
</tr>
<tr>
<td>Viral load (log₁₀ copies/ml)</td>
<td>4.5±1.2</td>
</tr>
</tbody>
</table>

*Note:* Data are number (% of patients or mean ± SD.
HAART = highly active antiretroviral therapy; AZT = zidovudine; 3TC = lamivudine; NVP = nevirapine; EFV = efavirenz; d4T = stavudine; BMI = body mass index; MUAC = mid-upper arm circumference; WHR = waist-hip ratio; LBM = lean body mass; FM = fat mass; BF% = body fat percentage.

**DISCUSSION**

In this study, subjects underwent significant changes in most of the anthropometric measures after just 24 weeks on HAART. Mean weight, BMI, MUAC, waist circumference, hip circumference, WHR, LBM, FM or BF% between baseline and the 24-week follow-up visit and changes in CD4 lymphocyte count. Change in CD4 lymphocyte count between baseline and 24 weeks was not significantly associated with any of the baseline anthropometric measurements, except for MUAC with which there was a modest but significant positive correlation (r=0.40; p=0.04).

Although the majority of the subjects gained weight during the follow-up period, some had a body weight which remained stable and others lost weight. This is in accordance with the results of the study by Saghayam et al. Some of our subjects gained significant amounts of weight (range 1.2 - 24.7 kg), with the majority of the weight gain in most subjects being attributable to an increase in muscle mass, which is associated with improved functional performance, and identifying ways of improving LBM that are both effective and feasible may therefore prove valuable. Possible explanations for the improvement in LBM observed in some of the subjects in this study with a stable body weight include improvements in muscle mass as a result of an increase in activity levels associated with an overall improvement in health after starting HAART, or dietary changes. In the 3
subjects who lost weight the loss was composed mostly of LBM, and this is well known to be prognostically unfavourable.6 Two of the 3 subjects who lost weight were known to live in food-insecure households and the other reported intentional weight loss.

From the results, it can be seen that the baseline CD4 lymphocyte count before HAART initiation appears to have an inverse relationship with change in BMI, FM, and BF% between baseline and the 24-week visit. Subjects with lower CD4 lymphocyte counts experienced greater increases in weight, BMI, FM, and BF%. The finding that subjects with more severe immunosuppression at baseline experienced greater increases in body weight on HAART is supported by the results of the study by Shikuma et al.10 In a study by Mwamburi et al.,9 changes in CD4 lymphocyte count after the initiation of HAART were associated with changes in weight, but others have found no relationship.7 In our study the anthropometric changes were not significantly correlated with changes in CD4 lymphocyte count. Larger studies of longer duration should be carried out to examine the changes in anthropometric measures that occur after the initiation of HAART and to describe more clearly the relationship between anthropometric measures and immunological response as well as the overall health of subjects.

Another noteworthy observation was the disproportionate change in circumference measures seen in some subjects. This may indicate fat redistribution, during which it is common for subjects to experience fat loss from the buttocks and extremities, and/or an increase in abdominal FM.13

The finding that such a large proportion of the subjects in this study had a BMI above the upper limit of the normal range and that a considerable number had abdominal fat accumulation, as indicated by the WHR and waist circumference measurements, is cause for concern, firstly because of the well-known health risks associated with overweight and obesity in the general population, which include type 2 diabetes mellitus, hypertension, respiratory difficulties and dyslipidaemia.5 Secondly, an

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**TABLE II. ANTHROPOMETRIC AND LABORATORY MEASURES AT BASELINE AND AFTER 24 WEEKS ON HAART**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Baseline (N=30)</th>
<th>24 weeks (N=27)</th>
<th>Change</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (kg)</td>
<td>63.7±16.0</td>
<td>68.2±15.0</td>
<td>3.4±5.8</td>
<td>0.006</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25.6±5.7</td>
<td>27.3±5.6</td>
<td>1.4±2.5</td>
<td>0.007</td>
</tr>
<tr>
<td>MUAC (cm)</td>
<td>28.4±5.1</td>
<td>29.8±4.4</td>
<td>1.1±2.1</td>
<td>0.009</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>84.5±11.6</td>
<td>88.3±11.2</td>
<td>3.3±6.4</td>
<td>0.012</td>
</tr>
<tr>
<td>Hip circumference (cm)</td>
<td>98.6±13.2</td>
<td>102.1±11.8</td>
<td>2.6±4.9</td>
<td>0.011</td>
</tr>
<tr>
<td>WHR</td>
<td>0.86±0.05</td>
<td>0.86±0.07</td>
<td>0.01±0.04</td>
<td>0.294</td>
</tr>
<tr>
<td>LBM (kg)</td>
<td>41.9±5.7</td>
<td>43.0±6.2</td>
<td>0.7±3.2</td>
<td>0.262</td>
</tr>
<tr>
<td>FM (kg)</td>
<td>21.8±11.2</td>
<td>25.2±9.5</td>
<td>2.7±4.5</td>
<td>0.005</td>
</tr>
<tr>
<td>BF%</td>
<td>32.2±9.7</td>
<td>35.7±7.0</td>
<td>3.0±5.2</td>
<td>0.006</td>
</tr>
<tr>
<td>CD4 cell count (cells/μl)</td>
<td>164±69</td>
<td>268±154</td>
<td>120±114</td>
<td>0.000</td>
</tr>
<tr>
<td>Viral load (log₁₀ copies/ml)</td>
<td>4.5±1.2</td>
<td>1.7±0.8</td>
<td>-2.7±1.2</td>
<td>0.000</td>
</tr>
</tbody>
</table>

BMI categories

- <18.5 (underweight) 2 (6.7) 1 (3.7)
- 18.5 - 24.9 (normal weight) 13 (43.3) 8 (29.6)
- 25 - 29.9 (overweight) 9 (30.0) 10 (37.0)
- ≥30 (obese) 6 (20.0) 8 (29.6)

Waist circumference ≥80 cm baseline
- 9 (30.0) 9 (33.3)

Waist circumference ≥88 cm baseline
- 9 (30.0) 11 (40.7)

WHR >0.85
- 17 (56.7) 10 (37.0)

Note: Data are mean ± SD or number (%) of patients. HAART = highly active antiretroviral therapy; BMI = body mass index; MUAC = mid-upper arm circumference; WHR = waist-hip ratio; LBM = lean body mass; FM = fat mass; BF% = body fat percentage.
above-normal BMI may mean that a large proportion of HIV-infected individuals may not seek care, and health care professionals may not identify individuals for HIV testing as a result of the common misconception that they are ‘healthy’ when in fact they may not only be HIV-infected but already eligible for HAART.

Although the risks of overweight and obesity in the HIV-infected population specifically, and especially in the era of HAART, are not known, because of the association between overweight and obesity and adverse health outcomes in the general population it seems prudent to ensure that subjects are cautioned against excessive weight gain. The issue of overweight and obesity warrants attention, and studies are urgently needed to determine the prevalence and significance of overweight and obesity in the HIV-infected population in South Africa. The optimal nutritional advice to be given to overweight and obese HIV-infected subjects remains to be determined.

This study had some limitations that need to be acknowledged. Firstly, only females were included in the study and the results therefore cannot be generalised to male subjects. Secondly, owing to the small sample size we were not able to control for potential confounding factors such as HAART regimen and clinical parameters, and the changes that were observed may therefore have been independently associated with other factors not analysed. We recommend that future studies include both genders and a large enough sample to allow for investigation according to HAART regimen, clinical staging and other morbidity factors to allow for the development of widely applicable guidelines.

In conclusion, the findings of this study demonstrate firstly the value of including circumference measurements and body composition assessment techniques as part of the assessment of nutritional status. The results show that merely following weight changes in subjects would mask underlying changes in body composition and changes in fat redistribution. We therefore suggest that programmes include waist and hip measurements and if possible BIA measurements, at least annually or ideally at 6-monthly intervals, in order to provide useful information to assist in patient management. Secondly, this study suggests that given that the majority of subjects who gained weight gained mostly FM and not LBM, there is a need for further research to develop interventions such as exercise training programmes to improve LBM and decrease abdominal obesity. The long-term aim of HIV care and treatment programmes should not merely be to obtain virological suppression but also to improve overall health and quality of life.

REFERENCES


Previously, the only clinical consequence of HIV viral replication was thought to be a declining CD4 cell count, and development of resistance if on antiretroviral therapy (ART). Several recent studies have dramatically changed that understanding. Continuing viral replication seems to play a role in a bewildering array of illnesses not usually associated with HIV, including a diverse number of cancers, as well as chronic liver, kidney and cardiovascular disease.

Viraemia used to be regarded as a necessary evil. In the 1990s, an undetectable viral load was more the exception than the norm in developed countries, owing to drug toxicity and poor adherence. Increasing evidence that persistent viraemia is linked to the host of long-term consequences described above has changed the game. In 2009, a detectable viral load should probably be regarded as the notional equivalent of active cigarette smoking, and tackled with the same vigour.

Luckily, the pharmaceutical industry has rapidly brought several new and exciting but expensive ARV agents to the marketplace, providing new options for those with the money to pay for them.

The rise of novel antiretrovirals (ARVs) has introduced a new evolutionary phase in HIV care. In developed countries, the 1980s and early 1990s were characterised by palliative care and opportunistic infection prophylaxis; the late 1990s by an attempt to use a limited and toxic antiretroviral arsenal effectively while cycling through high levels of resistance; and finally, the first half of this decade by working out the easiest-to-take regimens, using the steadily rising number of safer drugs. At present, there are 8 nucleoside analogues (NRTIs), 3 non-nucleoside analogues (NNRTIs), 10 protease inhibitors (PIs), and one each of the fusion, entry and integrase inhibitors to choose from, along with a new drug pipeline that targets both existing and new targets in the viral replicative cycle. The choice may seem quite vast, but the reality is that many of these drugs cannot be used simultaneously or in patients with extensive drug resistance. In addition, some drugs have unacceptable toxicities and are not favoured in current treatment regimens.

In developing countries, there are complex drug interactions between rifampicin and the azoles, which patients are often on at the time of ART. Side-effects to stavudine and nevirapine remain distressingly common. In addition, new insights on resistance, especially subtype C, which may compromise future options around tenofovir, have begun appearing. A recent developing world study demonstrating increased rates of NNRTI-based
regimen failure after single-dose nevirapine for prevention of mother-to-child transmission emphasised the clinical consequences of the low resistance threshold of these drugs. Drug resistance to any infectious disease in the presence of antimicrobial pressure is near inevitable, and needs to be factored into any treatment algorithm. In the case of HIV, the stakes are higher when cross-resistance is considered, as the treatment is lifelong, and treatment options in poorer areas are limited. Combinations of genotyping and phenotyping resistance testing remain prohibitively expensive for the developing world. Drugs that may overcome both primary and secondary resistance therefore become more important in both the developed and developing world scenario.

Essentially, Southern Africa needs safer, more effective and cheaper ART options.

Enter the classes of drugs with science-fiction names – the CCR-5 blockers, fusion inhibitors, integrase inhibitors, maturation inhibitors – as well as safer and more potent versions of existing classes, with chest-thumping names for trials, such as MOTIVATE, RESIST, TITAN and BENCHMRK. One ART advertisement even shows an HIV ‘meteor’ heading for a cellular planet, protected by a ring of the drug. Immediate results with these new therapeutics have left new-drug junkies open-mouthed, as patients with detectable viral loads for decades after being on every conceivable ART regimen are consigned to ‘undetectable’.

**INTEGRASE INHIBITORS**

These drugs block integrase, which mediates the insertion of HIV DNA into the genome. The integration process is complex, and there is interest in directing new drugs at several steps in the integration process, which includes the assembly of a ‘pre-integration complex’, processing with subsequent strand transfer, and the final step of assembling a viable piece of double-stranded DNA.

The first drug to hit the market in this class is raltegravir (Isentress; Merck Sharp & Dohme (MSD)), which has generated the kind of excitement among treatment experts last seen with the onset of access to tenofovir or efavirenz. The drug is currently under consideration by the South African Medicines Control Council (MCC), and may be registered in the first half of 2009. Registered in late 2007 by the US Food and Drug Administration and the European Medicines Evaluation Agency on the back of trials showing high efficacy in patients with significant resistance from prior regimens, the drug has also been used successfully in drug-naive patients, although it is not currently registered for this. Data from the BENCHMRK trial recently showed that raltegravir was comparable to efavirenz in treatment-naive patients after 96 weeks of treatment, with the advantage of a more favorable side-effect profile. Whether the benefit is sufficient to trigger a change in first-line prescribing is controversial, and guidelines still overwhelmingly favour efavirenz in drug-naive patients.

**Raltegravir** is dosed twice daily, has no food restrictions, and appears to have relatively limited impact on the different cytochrome systems. The drug interaction with rifampicin is under investigation, and caution will be required during co-administration in tuberculosis patients until more data are received. There is some excitement among basic scientists that raltegravir may decrease the size of the ‘latent pool’ of HIV-infected cells, although the clinical importance of this seems questionable.

However, the real excitement has been seen in those clinicians dealing with treatment-experienced patients, where the drug, when used with a new boosted PI, appears to control viraemia effectively and safely. Resistance assays are being developed, and early evidence suggests that there is cross-resistance with other agents in the integrase class.

The major questions that hang over the raltegravir head are side-effects and cost. As with all drugs, side-effects are still unclear, and the usual regulatory agency careful watching process is underway. It often takes several years for less common or long-term side-effects to become apparent – witness the highly publicised if controversial link between abacavir and myocardial infarction, only documented a decade after the drug became available. However, raltegravir has proved surprisingly popular, and a large number of patients have already been introduced to the drug in developed countries. Early safety data have been excellent, with no common serious side-effects. Initial therapy may be associated with mild gastrointestinal effects and dizziness, although the neuropsychiatric side-effects are significantly lower when compared with efavirenz in treatment-naive patients. However, there have been several reports of increased muscle toxicity and caution should be exercised in patients at risk of myopathy or rhabdomyolysis. The effect on lipid levels is minimal. By the time we have broad access to (or need) this agent in southern Africa, we should have a good idea of what sort of safety concerns we need to be on the lookout for.

More immediately of concern is the cost. At the current $9 a day this is prohibitive, even for private care. Competitor products are in development, with a drug called elvitegravir (from Gilead, of tenofovir fame), dosed daily and also with similar good preliminary data, which looks likely to be registered in the next few years but is unlikely to cost much less.

**NEW NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS (NNRTIs)**

Efavirenz and nevirapine are the ‘non-nuke’ backbone of almost all new initiations in the developed and developing world. NNRTIs are convenient, relatively non-toxic,
and highly effective. Concerns surrounding drug interactions, side-effects and efavirenz teratogenicity are unlikely to displace them from their role in first-line therapy for at least the next few years. The genetic barrier of this first-generation NNRTI is low, with resistance occurring rapidly and completely after a single mutation. Most virological failure patients therefore experience the loss of this class with their very first failure. It is also of concern that transmitted NNRTI resistance is well described and a growing problem in developed world settings.

With a lot less fanfare than the other new drugs, the new-generation NNRTIs have entered the fray. Etravirine (Intelence; Tibotec), a second-generation NNRTI, requires multiple mutations, and is effective in treating most patients who have failed efavirenz or nevirapine. Etravirine is interesting, as it was initially tested in conjunction with another experimental PI, a high-risk strategy for the pharmaceutical company. Toxicity profiles appear negligible so far, with rash and nausea the commonest symptoms.

Etravirine seems to retain activity even in the presence of several mutations, behaving more like an NRTI than an NNRTI in this regard. However, specific etravirine-associated mutations seem to occur more frequently in patients who have non-clade B virus and have been exposed to first-generation NNRTIs. Drug interactions appear to be significant and etravirine should not be administered in conjunction with boosted tipranavir, fosamprenavir or atazanavir and definitely not with unboosted PIs, thereby limiting its use in salvage regimens. It is not recommended for use alone with NRTIs in patients who are PI-naïve and have previously failed an NNRTI, owing to sub-optimal results in this group.

Complex to make, etravirine is likely to remain prohibitively expensive for some time. The expense is compounded by the fact that resistance testing and interpretation is likely to be needed before using the drug, limiting its application in our setting. Interpretation of resistance is complex, with initial local data (personal communication, Professor Wendy Stevens, National Health Laboratory Services) suggesting that additional data will be needed before we can confidently predict responses in our region. Coupled with the fact that the southern African epidemic is predominantly clade C, and that first-generation NNRTIs are used extensively in first line with suboptimal virological monitoring, means that the jury will probably be out on this drug for some time.

**CCR-5 INHIBITORS**

The CCR-5 blockers (less commonly called chemokine antagonists) act on the major receptor that facilitates entry of HIV into the cell. Observations that mutations within the gene that codes for this receptor appear to profoundly modify the ability of the virus to enter, have led to the development of several therapeutic molecules, altered chemokines and monoclonal antibodies. Development of these drugs was initially slowed after liver side-effects were observed, with one drug in the class, aplaviroc (GSK), halted despite initial promising results.

Pfizer’s maraviroc (the imaginatively named Selzentry in the USA; Celsentri elsewhere, licensed in 2007, and awaiting MCC registration in 2009) has been the first out of the starting blocks and has been approved in developed countries for treatment-experienced patients. Studies in these patients, done in record time to counter their competitors, have proven the drug performs well, and has a good short-term side-effect profile. The drug has been evaluated in head-to-head studies against efavirenz in naïve patients, but results have not been convincing, and it seems unlikely at present that the drug can compete with the non-nukes in first line as yet.

The major problem with maraviroc is the necessity for tropism testing. CCR-5 is not the only entry point for HIV, and the ‘tropism’ or predisposition determination for these alternative entry points requires an expensive and complex test, which is not foolproof. A patient with a CXCR4 tropism predisposition is much less likely to respond to the drug, so the test is essential. Resistance is usually characterised by a tropism switch to CXCR4, although this does not seem to have any direct immunological consequence. The drug also has a significant impact on the cytochrome systems, much like the PIs, with drug interactions with other ARVs and opportunistic infection medication, and requires dose modification in many common clinical circumstances.

An unexpected aside in one of the trials involving maraviroc may have special implications for our region. The MERIT study compared maraviroc with efavirenz in antiretroviral-naïve subjects. There was little difference in terms of antiviral activity, but those who were given maraviroc developed only one incident TB infection while those in the efavirenz group had six. Scientists are excited, and are exploring the biological plausibility of
this observation. Time will tell if this will strengthen the case for this drug, or possibly open up new TB prevention options.

Pricing of maraviroc is likely to be an issue, as with all these new drugs, and an access price locally has yet to be determined. Currently the drug is available under a section 21 MCC approval for just under $1 000 monthly, which is prohibitive. Already one developed country health care system (the Scottish National Health Service) has declined the use of these agents due to the cost.

The other potential CCR-5 blocker, vicriviroc, this time from Schering-Plough, has had a difficult time; an unexpected increase in malignancies, mainly lymphoma, was observed in one trial, and its predecessor, which is not structurally linked to vicriviroc, had unacceptable toxicity levels. This was counterintuitive, as patients with the previously described CCR-5 mutation are supposedly more protected against lymphoma (although the mutation seems to be implicated in progression of breast cancer), so this finding created consternation. There is some fear that this may be a class effect, but the strange correlation with cancer has not been seen with maraviroc. Subsequent statistical analysis suggested that the cancers were probably not linked. A theoretical link to West Nile virus suggested by another epidemiological study looking at CCR-5 mutations also stirred the pot, but no cases have yet been seen in treated patients. However, some clinicians are wary about this class of drug, which do not directly inhibit HIV replication, but rather play a more indirect effect on the immune system.

Entry inhibitors represent interesting candidates for pre-exposure prophylaxis from a biological plausibility standpoint (stopping the virus from penetrating at all, rather than arresting its development within the cell, as with current ART prophylaxis). If this concept turns out to be verified by trials, this use for this class of drug may turn out to be the most interesting yet.

**PROTEASE INHIBITORS**

For several years now, boosted PIs have formed the backbone of therapy after initial virological failure. Unpopular in first-line therapy because of their side-effect, metabolic and cost profiles, PIs have established themselves as robust and highly effective alternative agents, and are recommended in all second-line therapies in the developing world, with lopinavir/ritonavir (Kaletra) being the most popular. An alternative and competitively priced PI, atazanavir, is available and better tolerated, but requires co-administration with separate ritonavir, due to patients being held by different pharmaceutical companies. There is a more appealing option with the registration of Alluvia, Kaeltra’s heat-stable formulation. With the rise of new agents, many of the older PIs, including nelfinavir, saquinavir and indinavir, have fallen steadily into disuse. Treatment expectations with the newer PIs are so high that international and local guidelines recommend a zero tolerance to detectable viral loads when these agents are used. Protease mutations appear more complex than most other ART mutations, with a wide array of primary, secondary and background polymorphisms, some of which confer high-level resistance to the agent, and others that may confer hypersusceptibility. The newer agents both select for mutations which require weighting systems in order to assess the effect of the multiple mutations they select for, making interpretation complex and requiring experience. The realisation that not all resistance is equal, that boosted PI resistance may be more ‘forgiving’ of sub-optimal adherence, and that failure is rarely associated with significant PI mutations, has opened the way to effective third- and fourth-line regimens using these drugs, always in their boosted form.

New second-generation PIs darunavir (Prezista; Tibotec) and tipranavir (Aptivus; Boeringer-Ingelheim) both require boosting with ritonavir, but require a large number of mutations before they lose efficacy. The drugs carry the usual long list of drug interactions seen with PIs, making their administration complex.

Initial efficacy and toxicity data with boosted darunavir (approved by the FDA in 2006), when compared with Kaletra, are very encouraging, and Tibotec is positioning the drug as a serious competitor to lopinavir/ritonavir after demonstrating good results in heavily treated patients and in those with moderate resistance, as well as in PI-naive patients. Darunavir remains active in patients who are heavily treatment-experienced with demonstrated resistance to all other PIs, including lopinavir/ritonavir. In the TMC115 studies, 60% of subjects who had decreased susceptibility to tipranavir showed a decrease of more than 1 log in viral load after 24 weeks of treatment with darunavir, with over a third achieving complete suppression. This was clinically highly significant in the era before the advent of integrase inhibitors. There is some element of cross-resistance between darunavir and tipranavir, although half of isolates with darunavir resistance still demonstrated some susceptibility to tipranavir. At this point, the actual sequencing of PIs – which should we use first so as to preserve the subsequent ones? – is a matter of much debate among clinicians.

Darunavir/ritonavir is dosed at 600/100 mg twice daily and must be taken with food. It is both a substrate and an inhibitor of CYP3A and therefore has similar drug interactions to lopinavir/ritonavir. Among the severe side-effects reported are skin rash (including Stevens-Johnson syndrome). Darunavir contains a sulfa-moity and must be administered with caution in patients who are allergic to sulfa drugs.
Interesting studies using darunavir as monotherapy after an initial intensification phase are also underway, despite the disappointing results seen in the monotherapy studies with lopinavir/ritonavir. Other studies are looking at paediatric populations, and initial results have been very good in treatment-experienced children and adolescents.

Aspen, South Africa’s generic giant, has agreed to distribute darunavir (Prezista) in sub-Saharan Africa at a price of $3 a day, which remains expensive for the state sector but makes it an enticing option for managed care organisations.

Tipranavir is slightly older, registered in 2005 by the FDA for resistant patients and with a paediatric formulation registered in 2008. It is dosed twice daily with food, and requires a relatively high dose of ritonavir (200 mg twice daily) for effective boosting. Tipranavir and darunavir appear equally virologically effective. Drug side-effects are similar to other PIs in nature, with a curious report linking to the drug to intracranial haemorrhage still under investigation. However, the drug has also performed very well in salvage regimens, firmly establishing itself as an option in treatment-experienced patients.

CONCLUSION

ART clinicians and their patients have an impressive new armamentarium looming. However, the cost and unknown toxicities of these drugs mean that the longer we can preserve the first-line therapies we have, the better. For the developing world most, if not all, of these agents are currently unaffordable in the public and even the private sector. Toxicity data are often delayed, and will be widely publicised if significant, so we can afford to be cautious. For the small number of experienced patients who require these drugs, mechanisms exist for them to be accessed through the application (section 21) process set out by the Medicines Control Council.

First-line therapy, comprising two NRTIs and an NNRTI, is unlikely to change in the immediate future. In second line, the choice of boosted PI seems fairly evenly matched, although preliminary data suggest that the well-established lopinavir/ritonavir has some less toxic competitors, mainly from new PIs but potentially even from the other newcomers. While raltegravir looks increasingly attractive as a second-line alternative to existing choices, as does etravirine; close virological monitoring may be the answer to the relatively low genetic barrier of raltegravir. Use of the CCR-5 inhibitors is limited by their reliance on extremely expensive tropism assays and they will have little to no immediate place in the developing world unless both their pricing structure and their tropism assay reliance are resolved.

Debate rests as to how a third-line regimen should be structured, but it is likely to be expensive, if not particularly toxic, and will still require significant expertise on the part of clinicians. Optimal use of these agents would depend on expensive genotyping assays, beyond the reach of many public sector programmes in southern Africa.

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BIBLIOGRAPHY

A 33-year-old man was noted to be HIV positive in 2005 after a diagnosis of sputum-positive pulmonary tuberculosis (TB). He responded well to 6 months of standard TB therapy. The initial HIV diagnosis was made in Durban and he was lost to follow-up after moving to Cape Town.

In August 2007 he presented to a regional hospital in the Cape Town metropole with cryptococcal meningitis (cerebrospinal fluid culture positive for Cryptococcus neoformans, CLAT titre 1:2048). At this stage his CD4 count was 116 cells/μl. He was initially treated with intravenous amphotericin B for 10 days followed by oral fluconazole 400 mg daily for 8 weeks. This was then reduced to a maintenance dose of 200 mg daily. He was also commenced on co-trimoxazole prophylaxis. He was referred to a regional antiretroviral (ARV) roll-out clinic but did not immediately attend for follow-up. Instead, in late November 2007 he again presented to the regional hospital emergency service with meningeal symptoms. Lumbar puncture again demonstrated a lymphocyte-predominant CSF that was CLAT positive (titre 1:296). The repeat CSF culture was negative.

A preliminary pre-ARV assessment was performed during this admission and abnormal liver function tests (LFT) results were noted. He was not jaundiced and the liver profile abnormality was a mixed pattern with elevated transaminases and canicular enzymes, both approximately 2 - 5 times above the normal range (Table I). Synthetic liver function was preserved. Despite withdrawal of co-trimoxazole, the patient’s liver enzymes remained deranged and he was referred to our service for evaluation.

At evaluation, no history of alcohol, other drugs or toxin use was obtained. Clinically he was thin with no obvious lymphadenopathy or typical features of chronic liver disease. He had a modest hepatomegaly but no splenomegaly. He was pyrexial with a temperature of 38°C. An abdominal ultrasound scan demonstrated increased liver echogenicity, no biliary dilation, normal portal and hepatic vessels and no intra-abdominal lymph nodes or ascites. A viral hepatitis screen was negative. A repeat CD4 count was now 1 cell/μl. The pattern of liver enzyme abnormalities was unchanged. Of note on the chest radiograph were right upper lobe alveolar infiltrates.

An early morning sputum specimen was sent for TB assessment and all samples were negative for acid-fast bacilli. The initial sputum culture was positive for Streptococcus pneumoniae and he was treated appropriately.

A liver biopsy specimen demonstrated an unanticipated and uncommon finding of numerous intraparenchymal collections of histiocytes associated with numerous fungi in yeast forms. These were confirmed to be C. neoformans (Fig. 1). Additionally there was modest macrovesicular fatty change with no associated inflammation. A piece of the core of liver tissue was submitted for TB and fungal culture. The fungal culture was negative for cryptococcus, suggesting that the organisms were non-viable after the previous treatment.

After the biopsy findings, a diagnosis of sub-optimally treated disseminated cryptocoecosis was made. The patient received 2 weeks of intravenous amphotericin B followed by oral fluconazole. He improved both clinically and in terms of LFT results. He was discharged in late January 2008 and an appointment for counselling and commencement of ARV therapy was made. Three weeks


REFERENCES


The reasons for this are not clear, but may relate to the overwhelming presence of M. tuberculosis in our local setting.5 The second issue was the unexpected culture of MAC in this patient demonstrated the additional value of liver biopsy in that it provided tissue for culture. As many OIs involve disseminated infection, liver tissue is a potential source of tissue for culture.

In summary, this case highlights the potential value of liver biopsy in patients with advanced HIV and abnormal LFTs where there is a wide range of differential diagnoses. Provided the procedure can be performed safely, liver biopsy both enables demonstration of the histological pattern of injury accounting for the LFT abnormalities and provides tissue for culture to diagnose opportunistic infections. In this case, an accurate diagnosis could be made following readmission and enabled appropriate treatment to be initiated.

Acknowledgement: Dr Helen Wainwright, UCT Department of Anatomical Pathology, for liver histology review and images.

Table I. Liver Function Test Results

<table>
<thead>
<tr>
<th>Parameter (normal range)</th>
<th>Dec 07</th>
<th>Jan 08</th>
<th>Feb 08</th>
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<tbody>
<tr>
<td>TBil (0 - 17)</td>
<td>3</td>
<td>6</td>
<td>87</td>
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<td>ALT (0 - 40)</td>
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TBil = total bilirubin (μmol/l); ALT = alanine transaminase (IU/l); AST = aspartate transaminase (IU/l); ALP = alkaline phosphatase (IU/l); GGT = gamma-glutamyltranspeptidase (IU/l).

Fig. 1. Grocott stain of liver biopsy core demonstrating Cryptococcus neoformans.

The investigation and management of patients with advanced HIV in South Africa often poses a multitude of diagnostic and therapeutic challenges. LFT abnormalities are a frequent finding in HIV-positive patients, with previous studies reporting a prevalence ranging between 30% and 75%.1 Liver biopsy-based studies have demonstrated the benefit of liver biopsy as a useful diagnostic tool in the setting of advanced HIV with pyrexia of uncertain origin and/or hepatomegaly and LFT changes.4

The patient described demonstrates the above together with several other issues. Firstly the liver biopsy provided a clear histopathological diagnosis. The finding of a prevalent opportunistic infection (OI) such as C. neoformans in the liver has not commonly been reported in the literature despite the pathophysiological tendency for widespread dissemination of cryptococcus following entry via the pulmonary route. In our own local experience this is the first case in which we have demonstrated it in the liver.

Notably, the patient’s liver function progressively improved and he was discharged to a regional ARV clinic. He continues to do well, and recent LFT results are set out in Table I.

DISCUSSION

Later, before attending the ARV clinic, he was readmitted with a febrile illness. A chest radiograph demonstrated segmental right lower lobe consolidation with cavitation and right hilar lymphadenopathy. Sputum samples were now positive for acid-fast bacilli. Mycobacterium tuberculosis (MTB) was suspected.

All previous cultures were reviewed. Notably, the liver tissue as well as sputum previously submitted had cultured M. intracellulare. Retrospectively a modified Ziehl-Neelsen stain of the liver biopsy specimen was performed and was negative. The patient was commenced on rifabutin, clarithromycin and ethambutol and steadily improved. ARV therapy was commenced as an inpatient.

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The second issue was the unexpected culture of M. intracellulare, or MAC (M. avium complex) as it is more commonly referred to, from the liver tissue. The presence of multiple OIs is not unusual in patients with advanced HIV/AIDS. What is unusual is finding MAC in our setting. In the pre-ARV era MAC was a frequent finding on liver biopsy in patients with advanced HIV in the developed world; however, as has been demonstrated previously, MAC appears to be uncommon in our local setting.5 The reasons for this are not clear, but may relate to the overwhelming presence of M. tuberculosis in our HIV population. The culture of MAC in this patient demonstrates the additional value of liver biopsy in that it provided tissue for culture. As many OIs involve disseminated infection, liver tissue is a potential source of tissue for culture.

In summary, this case highlights the potential value of liver biopsy in patients with advanced HIV and abnormal LFTs where there is a wide range of differential diagnoses. Provided the procedure can be performed safely, liver biopsy both enables demonstration of the histological pattern of injury accounting for the LFT abnormalities and provides tissue for culture to diagnose opportunistic infections. In this case, an accurate diagnosis could be made following readmission and enabled appropriate treatment to be initiated.

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