SOUTHERN AFRICAN JOURNAL OF HIV MEDICINE

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Cover: *Children at Ukhanyo Primary School, Masiphumelele, celebrate World TB Day (24 March 2007) – photo by Dr Keren Middelkoop of the Desmond Tutu HIV Foundation, Cape Town. Photos elsewhere in this issue, all taken on World TB Day in Masiphumelele, are by Keren Middelkoop and Craig Whitty.*

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FROM THE EDITOR

It is with more than a twinge of nostalgia that I write this editorial for Journal 26. The first issue of the *Journal of HIV Medicine* was distributed at the Internal Aids Society Conference, Durban 2000. This issue will be distributed at the National Aids Conference, Durban 2007. Once again there is a wide variety of articles spanning epidemiology, guidelines and clinical case studies.

I am happy in the knowledge that the *Journal* has found a place on the desks and in the hearts of practitioners in our region. It has I believe, achieved, a unique branding, look and feel.

I am standing down as Editor with this edition, but I am secure in the knowledge that the *Journal* will continue to flourish in the very capable hands of the new Editor, Professor Linda-Gail Bekker. I wish her and her editorial team the very best for the future.

DES MARTIN
Editor

MESSAGE FROM THE EXECUTIVE

It's been a topsy-turvy few months in the HIV prevention world. Two major circumcision trials were interrupted because the benefit of male circumcision was so marked. At the same time, two microbicide trials were stopped, one because of a low HIV incidence rate, making the trial impossible to complete, and another more recently that suggested no benefit from microbicides, and possibly even harm. The media storm over the ending of the microbicides trials is unfortunate, as the news reports referred to 'guinea pigs' and poor oversight, though there was no real proof of any wrongdoing by the scientists.

All this is very frustrating, leaving clinicians and public health policy makers with very few biological interventions to prevent HIV. Mother-to-child prevention works well but is poorly implemented, ditto for post-exposure prophylaxis for sexual assault; condoms work if used consistently, but very few people use them consistently; and circumcision is still trying to find its place. A useable vaccine looks years away. Luckily, a novel microbicide made of seaweed (!) is being tested in phase three trials, and results are expected by the end of the year.

In the wake of the microbicide criticism in some of the media, we must continue to insist on rigorous clinical trials. Our countries have been under siege by non-scientific quacks and opportunists for too long to retreat from good science.

FRANCOIS VENTER
President

PENNY PENHALL

'Southern African HIV Clinicians Society, Penny Penhall speaking, how may I help you?' Countless numbers of members who telephoned the Society would have been greeted by those words. Behind them was a person who dealt with a diverse range of requests, complaints and enquiries, always in a polite, caring and helpful way. I have received countless compliments on how helpful Penny had been in resolving an issue. It is difficult even to begin describing what she has meant to the Society, and the crucial role she has played in its development and maturation – her contribution has been enormous.

Penny comes from a nursing background, where she excelled, having received a number of academic awards. Her desire to contribute in the larger health care arena led her to become interested in the field of HIV/AIDS. It was fortuitous, therefore, that at the establishment of the Society in 1998 she was available to become involved in the crucial early phases. The beginning was humble – Penny started work in a shared office, and as I was President of the Society at the time, we would meet two mornings a week for a couple of hours to carry out the necessary administration. As the Society grew, a permanent office was secured and Penny started working full time for the Society. In the early days Penny did everything, and I mean everything! Answering the telephone, office administration, secretarial duties, writing grant proposals, arranging Society meetings, dealing with funders, organising conferences – she did the lot! Her work on the *Journal*, however, deserves special mention. This became our special project and I, as Editor, benefited enormously from Penny's expertise in the editing and publishing arena. The look and feel of the *Journal* as it is today is largely due to Penny's vision and expertise.

Over time the Society grew to its present size with 11 000 members and 29 active branches. The Society's activities expanded, and it became necessary to increase our capacity. Samantha Klusener, Pat and Jean Solan and more recently Venie Pillay came on board to assist in the activities that hitherto had been carried out by Penny alone. If I were to reflect on Penny's strengths they would include patience, meticulous attention to detail, an enormous work ethic and readiness always to 'go the extra mile'. This was particularly evident in dealing with the editorial deadlines of the *Journal*.

Penny has decided to take a break (she so richly deserves a rest) and would like to explore other challenges in the future. I know that whatever she decides to do she will give it her all and make it a success.

For me it has been a privilege working with Penny for the past eight years. She has taught me an enormous amount, and I know that I am joined by Francois, the members of the executive committee and all Society members in wishing her well in the future.

DES MARTIN
Editor

DEBATE

TB OR XDR TB, SHOULD THAT BE THE QUESTION?

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The emergence and recognition of extensively drug-resistant tuberculosis (XDR TB) in South Africa led to a wave of panic fuelled by media hype. The response was predictable: meetings, circulars and finally a seven-point emergency action plan.[1] Fortunately *Mycobacterium tuberculosis* (TB) replicates slowly, as very little seems to have happened in the 5 months since the proposal of the seven-point plan.

The seven-point emergency action plan for XDR TB is based on the seven-point plan devised for MDR TB in the 1990s.[2] The emergence of XDR TB is a consequence of the earlier plan's failure. Are we doing any better this time?

THE SEVEN-POINT PLAN

1. RAPID SURVEYS TO ASSESS THE CURRENT PREVALENCE OF XDR TB

The only comprehensive survey for South Africa conducted during the current HIV pandemic produced figures of 39% for MDR TB and 6% for XDR TB.[3] These figures were for a single small region in KwaZulu-Natal, and until comprehensive surveys are conducted nationally one can only speculate on the true extent of the problem in South Africa.

Hospital budgets are stretched and the further financial burden of routine culture and drug sensitivity testing on all cases of suspected TB cannot be borne by individual institutions. Limiting TB culture and susceptiblity testing of patients with persistent acid-fast bacilli (AFB) and retreatment cases in accordance with the National Guidelines will not provide the information required. In the KwaZulu-Natal series the median time from sputum collection until death for XDR TB cases was 16 days, leaving no time to fail treatment. Fifty-five per cent of the XDR TB cases had no history of prior TB. Central funding is required for the culture and drug sensitivity testing of all suspected TB cases nationwide to define the true extent and location of the problem.

Any intervention aimed at addressing a problem the extent and distribution of which is unknown will not be able to be assessed and may squander time and money. The cost of conducting a comprehensive national surveillance programme may be better spent on improving the current TB treatment programmes. This strategy will decrease drug resistance even if the extent of the problem is not known.

XDR TB is defined as an isolate of TB resistant to isoniazid (INH) and rifampicin (multidrug-resistant tuberculosis) plus any fluoroquinolone and at least one of three injectable second-line agents (i.e. amikacin, kanamycin or capreomycin).

2. ENHANCE LOCAL LABORATORY CAPACITY TO CARRY OUT CULTURE AND DRUG RESISTANCE TESTING

Laboratories are already strained by the current load of specimens and need to honestly assess their capacity to deal with a much larger volume if routine culture and susceptibility testing is to be advocated. Quality assurance and reproducibility is imperative so that clinicians may have confidence in the laboratory results. Laboratories should have the expertise and equipment available to perform the services they offer.

There is currently no system whereby clinicians are provided with a monthly list of culture-positive results for their hospital. Lack of this seemingly basic information means that hospitals are unable to identify and trace culture-positive patients who have not returned for follow-up.

Laboratory services need to take more responsibility with regard to the notification of clinicians or hospitals of positive TB culture results. A step in the right direction is the fact that the laboratory now contacts the clinician if a culture is found to be MDR TB. This needs to be extended to all positive TB cultures.

3. INCREASED TRAINING OF PUBLIC HEALTH STAFF TO IDENTIFY, INVESTIGATE AND TREAT XDR OUTBREAKS

Training and education needs to involve staff who manage TB patients and needs to focus on the control of all TB and not just XDR TB, as our TB incidence of 718/100 000[4] suggests that

South Africa's national TB control programme is not functioning. Without routine surveillance and a central point for all culture results, outbreaks of XDR TB will be missed because no specific clinical features have yet been identified that may alert clinicians to suspect XDR TB.

4. IMPLEMENTATION OF INFECTION CONTROL PRECAUTIONS

Infection control should be more than just a sign on the door. Public sector hospitals often face a large TB burden, and are required to manage an excessive number of patients with limited resources. As an illustration, a large tertiary hospital in Gauteng Province registered 6 992 cases of TB for 2006 – just under 20 new TB cases daily (personal communication). At this hospital over 100 medical patients are admitted daily via a 32-bed admission ward. Only 6 single-bed cubicles are available for the isolation of general medical patients. Medical staff at this hospital have no access to P95 masks. There are no ultraviolet lights or ventilatory control systems in any of the medical wards. Given the patient numbers and available facilities, no meaningful infection control is possible.

5. INCREASED RESEARCH SUPPORT FOR DRUGS TO TREAT XDR TB

We currently have highly effective short-course therapy available to treat TB. In South Africa nationally we achieve only a 54% cure rate for new smear-positive TB cases.[4] Some provinces are unable to cure a third of their TB cases.

There is an urgent need to develop drugs to treat the few patients with confirmed XDR TB. However, more drugs and more complex regimens will be of little use overall until we start to treat new smear-positive cases adequately. The introduction of new drugs into an already failing programme is likely to result in more resistant cases than they would treat.

6. DEVELOPMENT OF RAPID DIAGNOSTIC TESTS FOR TB

Cost will be the deciding factor when these tests are developed. Improved diagnosis is, however, of little benefit if the TB diagnosed is not treated adequately and cured.

7. ACCESS TO ANTIRETROVIRAL THERAPY

Antiretroviral therapy (ART) decreases the incidence of TB dramatically. This decrease is dependent on the absolute CD4 count.[5] To decrease the incidence of TB in South Africa we need to increase voluntary counselling and testing (VCT), clear backlogs at ART clinics, shorten the time from HIV diagnosis to commencement of ART, and campaign for a CD4 count higher than the current 200 to qualify for ART. ART in prisons, which are notorious for high TB incidence, is essential.

Other considerations include assessing whether we are not inadvertently encouraging resistance through well-meaning practices. The use of fluoroquinolones not only delays the diagnosis of TB but may promote the resistance to this class of second-line TB agents.[6] These findings are worrying given the liberal use of ciprofloxacin for diarrhoea in HIV-positive patients.

Isoniazid (INH) prophylaxis is highly effective, but the risk of inducing resistance needs to be seriously considered, particularly in a population group where proving a patient does not have active TB is as difficult as proving they do.

There are still questions that need to be answered with regard to the current treatment regimens in our patient population. Rifampicin may not be as well absorbed when part of fixed-drug formulations as when administered as a single agent.[7] Rifampicin's absorption is significantly decreased in HIV seropositive patients, particularly those with chronic diarrhoea.[8] The possible induction of widespread rifampicin mono-resistance would make short-course therapy ineffective. Large pharmacokinetic and pharmacodynamic studies are needed in our patient population to determine whether we are achieving the desired drug concentrations.

XDR TB is the end of a spectrum of a man-made problem and a result of poor TB treatment. The MDR/XDR TB problem can be overcome (even without quantifying it) by treating TB and HIV adequately, ensuring patient compliance with directly observed therapy, and practising adequate infection control measures in our clinics, hospitals, prisons and communities. These measures have been shown to not only decrease overall TB incidence but also decrease the prevalence of MDR TB in both HIV-seropositive and seronegative patients.[9]

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CLINICAL

NON-DIAGNOSTIC AIDS-ASSOCIATED MALIGNANT NEOPLASMS

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Acquired immunodeficiency syndrome (AIDS) malignancies are a well-recognised and potentially lethal consequence of the disease. Three malignancies have shown an increased incidence and qualify as AIDS-defining conditions when they occur in conjunction with HIV infection: Kaposi's sarcoma (KS), non-Hodgkin's lymphoma (NHL), including primary central nervous system lymphoma (PCNSL), and invasive cancer of the cervix. Data from the AIDS-Cancer Match Registry Study Group[1] demonstrate the relative increased risk for the development of the three current AIDS-defining cancers, but also suggest an increase in Hodgkin's disease (HD) and, to a lesser degree, anal carcinoma, testicular seminoma and lip cancer. Highly active antiretroviral therapy (HAART) has exerted an effect on the incidence of malignancies. Since its implementation the incidence of KS and NHL has declined substantially, but there has been no major change in the incidence of cervical cancer or Hodgkin's disease.[2] The most common source of morbidity and mortality from AIDS has been opportunistic infections (OIs). Since the improvement in survival of patients with HIV infection, due to better prevention, the treatment of infectious complications and HAART, there appears to have been an increase in the incidence of malignant tumours, in particular those non-diagnostic of AIDS.

Certain principles common to the treatment of HIV-infected patients with cancer apply to various malignant conditions. Treatment of such patients is complex and requires knowledge and understanding of both oncology and HIV infection.

Problems encountered while treating patients with malignancy include:

- Immunosuppression induced by chemotherapy can further compromise the immunocellular deficit of HIV-infected patients and might facilitate the onset of OIs and/or the evolution of the HIV infection itself.
- In patients with non-AIDS-defining malignancies, the CD4+ count is usually normal or slightly decreased at diagnosis, but may become severely depressed during and after treatment, resulting in a higher susceptibility to OIs.
- HIV-associated leukopenia, due to HIV-myelodysplasia or nucleoside analogue therapy, makes the administration of conventional dosages of chemotherapy difficult.
- Tolerance to chemotherapy in HIV-infected patients is generally poor and requires frequent dose reductions and/or delays in therapy.

The goals of cancer therapy, curative versus palliative, and the status of the underlying HIV infection must be evaluated in each individual case (Table I). Treatment should include therapy for opportunistic infections (OIs) and the underlying HIV.

TABLE I. GUIDE TO MANAGEMENT OF PATIENTS WITH NON-AIDS-DEFINING MALIGNANCIES

Immune system	Characteristics		Treatment
Intact	CD4+	> 200 cells/µl	Treat as if HIV negative
	OIs	Absent	Avoid wide RT fields
	Survival	Years	
Intermediate	CD4+	50 - 200 cells/µl	Poor tolerance to RT and CT Restrict RT fields Avoid CT
	Downward trend of CD4+		Treat OIs
Poor	CD4+	< 50 cells/µl	Palliation
	OIs	Life-threatening	Pain
	Survival	Months	Bleeding
			RT Short course Single fraction

OIs = opportunistic infections; CT = chemotherapy, RT = radiation therapy.

HODGKIN'S DISEASE

HD is the most common non-AIDS-defining tumour. The relative risk for HD in HIV-infected patients is consistent from study to study.[3,4] Although evidence suggests that HD might be associated with HIV-infected intravenous drug users, it does not appear to be restricted to this group only. The relationship between HD and HIV remains controversial and is not clearly understood. Despite these findings, it has been argued that both AIDS and HD affect patients in the 3rd and 4th decade of life, and that the association is merely coincidental. The relative risk for the development of HD in HIV-infected individuals varies from 7.9 to 8.5 in different studies.

However, when HD occurs, the presentation of disease in the HIV-infected patient differs from that in the HIV-negative individual. Investigators have noted that AIDS-HD is likely to

appear in younger patients, with a higher prevalence in males, and more advanced disease, stage III or IV (75 - 89%), at presentation. A higher percentage have B-symptoms (83%), which include night sweats, unexplained weight loss of more than 10%, pruritus and Pel Ebstein fever, and extranodal disease (63%), and patients are less likely to be cured (response rate 44 - 79%).[5] AIDS-HD is characterised by the predominance of unfavourable subtypes, with mixed-cellularity or lymphocyte-depleted (53 - 63%) the most frequently diagnosed histological types. A high frequency (80 - 100%) of Epstein-Barr virus (EBV) has been identified in tissue from HIV-infected HD patients[6] and might represent a factor involved in the pathogenesis of HIV-associated HD. Data from Carbone *et al.*[7] display the bcl-6 syn-1 positive Reed-Sternberg phenotype HD cells, reflecting the post-germinal centre B-cell origin in the HIV-infected population. In contrast to the general population, HD Reed-Sternberg cells derive from germinal centre B-cells.

TREATMENT

The optimal therapy for AIDS-HD has not been defined. Considering that HD is an earlier manifestation of HIV infection than NHL (higher CD4+ cell count at presentation), the treatment approach for the two entities might be different (Fig. 1). Most patients present with advanced disease and have been treated with combination chemotherapy such as ABVD (doxorubicin, bleomycin, vinblastine and dacarbazine), but response rates remain dismal. Tolerance to chemotherapy has been poor and frequent dose reductions and/or delays in therapy are required. Response to therapy is far below that seen in the general population with HD, with a reported 1.5 years median overall survival. In the HIV-negative population more than 80% of patients with HD are alive at 10 years.

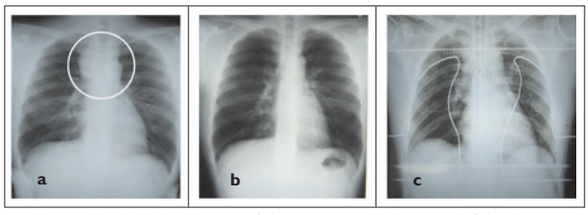

Fig. 1. Hodgkin's disease (a) at presentation, and (b) after 4 cycles of chemotherapy. (c) Simulator film for radiation therapy.

A study from the M D Anderson Cancer Center reported a 5-year overall survival rate of 54% with combination therapy (chemo- and radiotherapy) in AIDS-HD patients.[8] In an attempt to improve response and survival rates, Zittoun *et al.*[9] conducted a study with HAART-EBVP (epirubicin, bleomycin, vinblastine and prednisone) and *Pneumocystis carinii* pneumonia prophylaxis. Results of the trial showed an improved complete response rate of 74%. The 3-year disease-free survival and 3-year overall survival rates were 53% and 32% respectively, with the cause of death HD progression and OIs in 48% and 9% of patients. A prospective phase II study using a short-term Stanford V regimen with adjuvant radiotherapy showed this to be an active and feasible regimen in the setting of AIDS-HD, and concluded that the use of concomitant HAART does not increase chemotherapy-related toxicity.[10] Owing to the aggressive nature and advanced stages of AIDS-HD, more effective combined systemic anti-cancer and HAART therapy is required and should be used to improve the response and disease-free survival of AIDS-HD patients.

ANAL CARCINOMA

Several reports have suggested a slight increase in the incidence of squamous cell cancer of the anus associated with the HIV epidemic.[11] It is important to note that anal cancer was on the rise among homosexual men before the AIDS epidemic, owing to anogenital warts and sexual transmission of the human papillomavirus (HPV).[12] A high incidence of the human papilloma 16-type virus is associated with high-grade intra-epithelial neoplasia (AIN) and invasive cancer. It appears that HIV-induced immunosuppression allows reactivation of HPV, which leads to epithelial abnormalities. The incidence of AIN is significantly higher in homosexual men with HVP (61%) than in heterosexual men with HVP (4%). The incidence of anal cancer in HIV-positive men has been estimated at 70 per 100 000 persons per year.[13] However, it is unclear whether the increase in anal cancer is directly linked to HIV alone.

TREATMENT

Anal cancer is very sensitive to combined-modality treatment (CMT) with chemoradiation therapy and is a highly curable cancer with a 65 - 75% long-term survival rate in the general population. Data suggest that HIV-infected patients with anal cancer should be managed with the same treatment as HIV-negative individuals.[14]

Two phase III randomised trials by the European Organization for Research and Treatment of Cancer (EORTC) and the Radiation Therapy Oncology Group (RTOG) showed the benefit of adding chemotherapy to radiation and led to the general acceptance of 5-fluorouracil/mitomycin C and radiation therapy as the standard of care.[15,16] Radiation fields are designed to cover the main lesion, inguinal nodes, and low pelvic nodes. In patients with advanced HIV (CD4+ counts < 200/µl) mitomycin C should be withheld owing to the potential for severe myelosuppression and haemolytic-uraemic syndrome. There is evidence that HIV-infected patients who require therapy breaks (> 10 days) from chemoradiation due to severe skin reactions (Fig. 2) and dose reductions due to chemotherapy-related neutropenia have a higher incidence of local recurrence and a shorter survival.[17] In several small trials 40 - 80% of patients remain disease free, with a median follow-up ranging from 8 to 38 months. Prophylaxis against OIs and HAART is highly recommended during this period of potential iatrogenic immunosuppression.

For patients with advanced disease whose life expectancy is measured in months, a palliative approach is appropriate. The main goal is to relieve pain and bleeding, allowing patients to maintain their dignity and quality of life. A short course of radiation is well tolerated and recommended. Great care should be taken not to irradiate bowel unnecessarily in a

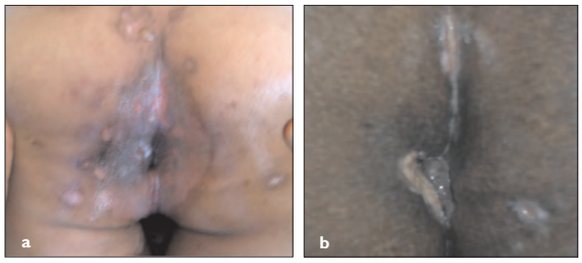

Fig. 2. Anal cancer: (a) skin reaction during radiation therapy, and (b) 6 weeks post radiation therapy.

population that might already be suffering from diseases such as chronic diarrhoea due to *Cryptosporidium* infections. As patients continue to live longer because of improved antiretroviral and prophylactic therapy, a rise in the incidence of invasive anal cancer is expected, which argues for better surveillance and screening for anal squamous intraepithelial lesions by anoscopy, cytology, and polymerase chain reaction (PCR) for HPV.

OTHER MALIGNANCIES IN THE HIV SETTING

HIV infection promotes immunosuppression which in turn fosters the development of malignancies. For most cancers, the higher prevalence is probably attributed to lifestyle factors among people with HIV. Malignancies may occur for reasons unrelated to immunosuppression, such as smoking and exposure to sexually transmitted HPV. As the AIDS epidemic advances, other tumours are increasingly seen in HIV-infected patients, including testicular cancer, lung cancer and basal cell carcinoma of the skin.

TESTICULAR CANCER

Recent data indicate that HIV-positive men have a significantly higher incidence of testicular cancer than the general population.[18] An Italian series of HIV patients with testicular germ cell tumours (GCT) suggested that the association between testicular cancer and HIV is not directly related to immune function.[19] The increase in seminoma was seen predominantly in homosexual males and white men. The majority of HIV-infected patients with GCT tolerate standard chemotherapy well and the majority obtain cure rates similar to those in the general population (Fig. 3). Treatment should include therapy for the underlying HIV and opportunistic infections (OIs).

LUNG CANCER

Epidemiological data do not support an increased incidence of lung cancer in the HIV-infected population. Tobacco smoking seems to be the major carcinogenic agent in both the HIV-infected and the general population. However, different features of lung cancer are observed in HIV-infected patients. The median age at presentation is younger, with adeno-carcinoma being the predominant histological subtype. More than 70% of HIV patients present with advanced stages of disease, including 55% with metastatic disease at the time of

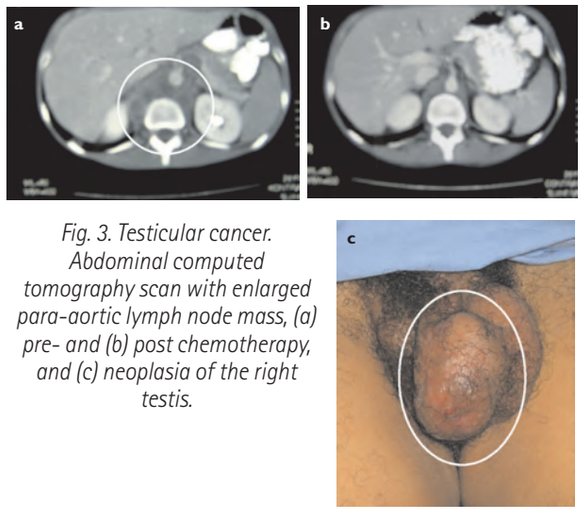

Fig. 3. Testicular cancer. Abdominal computed tomography scan with enlarged para-aortic lymph node mass, (a) pre- and (b) post chemotherapy, and (c) neoplasia of the right testis.

diagnosis.[20] Survival of HIV-positive patients with lung cancer remains poor, with a median survival of 6 months and only 10% of patients alive 1 year after diagnosis. If the HIV is under control, lung cancer should be managed with the same therapeutic strategies as in the general population.

PAEDIATRIC MALIGNANCIES

A 2.5% incidence of cancer in children with AIDS was observed by the AIDS-Cancer Match Registry Study Group for children younger than 14 years. Children who develop AIDS appear to have an increased risk of developing malignancies of the same type as adults, particularly non-Hodgkin's lymphoma (NHL) and leiomyosarcoma.[21] Burkitt's lymphoma was the most common lymphoma subtype and was diagnosed at a median of 14 months after the onset of AIDS. Kaposi's sarcoma was diagnosed within 2 years of the diagnosis of AIDS, and leiomyosarcoma tends to appear several years after the onset of AIDS.

CONCLUSION

Epidemiological reviews have failed to show a significant rise in the incidence of other malignancies in the HIV/AIDS setting.[22] With the improvement in antiretroviral therapy and appropriate prophylaxis for OIs, life expectancy for patients with AIDS will continue to improve. Consideration should be given to the use of HAART and appropriate prophylaxis for OIs during treatment with radiation and/or chemotherapy for any of these diseases.

Data regarding the influence of HAART on the prognosis of malignancies remain difficult to interpret, with some studies claiming improved survival, e.g. for patients with NHL,[23] whereas others claim no influence. Therapeutic decisions should be based on the HIV patient's current location on the timeline of his or her disease. Patients with CD4+ counts above 200 cells/µl tolerate anti-neoplastic therapy as well as the general population but may suffer from long-term bone marrow and bowel toxicities. While HAART has improved morbidity and mortality in HIV-infected patients, malignant neoplasms and their successful treatment remain a challenge.

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CLINICAL

INCREASING THE SCOPE AND INTENSITY OF INTERVENTIONS TO PREVENT HIV INFECTION IN INFANTS: BEST INTERESTS OF WOMEN AND CHILDREN

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Key messages:

- There is a mismatch between the HIV prevention needs of children and the quality and scope of prevention of mother-to-child transmission (PMTCT) services.
- Although near-elimination of paediatric HIV has taken place in many settings, PMTCT programmes in Africa have little impact so far.
- Given that it is in the child's best interests to detect exposure to HIV shortly after birth and to institute preventive interventions, routine HIV testing may be justified for all infants born to women of unknown HIV status.
- HIV testing for women at child health and immunisation clinics would enable more women to benefit from knowing their status and to receive infant feeding counselling and support.

This year another 460 000 children were infected with HIV in sub-Saharan Africa,[1] signalling an ongoing failure of programmes for PMTCT of HIV and the need to revise existing strategies. Despite initial energetic promotion, in recent years PMTCT has slipped down the policy agenda and coverage of these services remains below 10% in most African countries.[2] Overall impact of current PMTCT programmes on HIV-free survival among infants at a population level is unknown but likely to be low.[3,4] In contrast, in many other settings the risk of transmission is reduced to below 2%, with near-elimination of paediatric HIV.[5-7] In this paper we critique PMTCT strategies used in Africa and argue they require urgent revision. Under-utilised opportunities to prevent HIV infection in infants around childbirth and during breastfeeding are also highlighted. Interventions during chidbirth and postpartum would broaden the present antenatal focus of PMTCT programmes.

BENEFITS OF EARLY KNOWLEDGE OF HIV STATUS

HIV infection will declare itself, commonly with a severe illness that has substantial morbidity and mortality. The earlier in HIV disease that people become aware they are infected, the greater the benefit of care and treatment interventions. Further, to prevent transmission of a communicable disease, infected individuals should be identified as soon as possible after acquisition. Timely diagnosis of HIV confers considerable benefits to the individual and the wider community by facilitating access to care and prevention interventions, and changes in behaviour that accompany knowledge of status.[8,9] Within an enabling policy environment, the role of health workers is to identify early HIV disease and to maximise the benefits of knowing one's status for the infected individual and their susceptible sexual partners and children. Nowhere is this more clearly illustrated than in PMTCT programmes.

Each encounter with a woman in maternal and child health services is an opportunity for the woman to benefit from knowing her HIV status and to prevent further transmission. While the advantages for infants in being HIV-free are implicit, the benefits for women of having an uninfected child need to be highlighted. When giving pre-test information, health care workers should ensure that women are adequately informed of the benefits of PMTCT interventions, and of the emotional and financial consequences of having an HIV-infected child. However, many opportunities to benefit from knowing HIV status are missed with the current emphasis on the individual's right to decline testing and the potential harms associated with testing. The epidemic-long adoption of this approach has, paradoxically, undermined the individual's access to interventions to secure their right to health and that of their sexual partners and children. After decades of over-mystifying HIV testing, the pendulum has slowly swung to principles of public health accompanied by attempts to simplify testing and counselling procedures.[10,11]

Additional efforts to ensure that women directly benefit from PMTCT programmes may increase their acceptability and uptake. Renaming and remarketing of these programmes may be necessary. The name PMTCT ignores men's role in paediatric HIV infection, and fails to acknowledge that women are more than just mothers, and require maximum benefits from an HIV diagnosis, preferably made early in their HIV disease.

DUAL STANDARDS OF CARE: THE OUTCOME GAP

Initiating antiretroviral therapy (ART) for pregnant women helps ensure that benefits of PMTCT programmes accrue to both women and infants. Though given high priority by PMTCT guidelines,[12] ART for pregnant women with indications for treatment has been inadequately operationalised. Guidance is needed on practical aspects of developing well-functioning linkages between antenatal and ART services. For pregnant women, accelerating initiation of ART is often necessary to decrease MTCT risk. Difficulties with timely initiation of ART during pregnancy are compounded by health-seeking patterns, with women often first attending antenatal care late in pregnancy. Measuring CD4 cell counts at the first antenatal visit appears particularly important in reducing delays.[13]

So far, efforts to prevent HIV infection in children have focused on providing short-course ARV regimens for MTCT prophylaxis, most commonly single-dose NVP (sd-NVP). In several African countries, studies have recently investigated the role of triple-ARV regimens used solely for MTCT prophylaxis.[14-17] These regimens are given to women without indications for ART, and are stopped after childbirth (or after weaning). Such interventions bridge the gap in outcomes between infants born to women in Africa (including the South African private sector[18]) and those in the USA, Europe, Brazil and other settings. Long-course triple ARV prophylaxis is the standard of care in high-income countries (since 1998 in the US[19]) as well as in middle-income countries of South America, where more than 90% of HIV-infected women receive triple-ARV prophylaxis.[5,20] Disparities between infant outcomes illustrate stark global inequities: in Africa use of sd-NVP entails a risk of MTCT of about 12%, while elsewhere triple-ARV regimens reduce transmission to below 2%, with little viral resistance. Even in the South African private sector, women receive a standard of care below that provided in the public sector in countries like Brazil.[18]

A recent study in Johannesburg showed that risk for MTCT in women who initiate ART during pregnancy for their own health is lower than in women who do not have indications for ART and receive sd-NVP.[13] This demonstrates the limitations of sd-NVP – infants born to women with high CD4 cell counts had almost a threefold higher risk of HIV infection than infants born to women with advanced HIV disease (at substantially higher baseline risk of MTCT).

Several studies are investigating whether ARV drugs, given either to breastfeeding women or infants, reduce MTCT during breastfeeding.[21] This offers a promising alternative for a problem that causes tremendous difficulties wherever replacement feeding is not feasible. ARV drugs have been shown to reduce MTCT during pregnancy and childbirth in randomised trials, and in observational studies to reduce HIV acquisition after sexual or occupational exposure. Evidence from randomised trials that ARV drugs reduce postpartum transmission is expected in the next years – about 14 years after demonstration that ARV drugs reduce antenatal and intrapartum transmission.

PMTCT ENTRY: THE CHILD'S BEST INTERESTS

In addition to using more effective ARV prophylaxis, to improve impact of PMTCT programmes, several interventions around childbirth and during breastfeeding warrant consideration. These interventions aim to complement and broaden the current antenatal focus of PMTCT programmes. Shortly after childbirth, identifying HIV-exposed infants born to women who have not accessed PMTCT services (either because these services are unavailable or because they declined the offer of HIV testing) would enable HIV-exposed infants to benefit from interventions to reduce their risk of acquiring HIV. Rapid HIV tests, using whole-blood specimens from heel sticks, are especially suited to testing newborns for HIV exposure. Giving ARV post-exposure prophylaxis to infants born to women who did not receive ARV drugs during pregnancy or labour has been shown to reduce MTCT in a randomised trial in Malawi[22] and in South Africa.[23] If ARV prophylaxis is delayed more than 2 days, it is unlikely to have any benefit.[24]

HIV testing is considered part of essential care around childbirth for women of unknown HIV status.[12] In women who decline HIV testing, safeguarding the wellbeing of the child needs to be balanced with protecting the woman's right to privacy. The UN Convention on Rights of the Child (CRC) provides guidance on achieving this balance, stating: 'In all actions concerning children, whether undertaken by public or private social welfare institutions, courts of law administrative authorities or legislative bodies, the best interests of the child shall be a primary consideration.'[25]

South Africa is a signatory of the Convention and in 1995 ratified it, making it legally binding.[26] With evidence that post-exposure prophylaxis for infants is effective, and the high mortality associated with childhood HIV infection, we argue that in the best interests of the child, HIV exposure should be detected, irrespective of the mother's wishes. Using these arguments, consistent with the CRC, the overarching priority is to identify infants exposed to HIV and to deliver interventions to reduce risk of HIV acquisition. With adoption of this policy, all infants born to women of unknown HIV status would be routinely tested for HIV shortly after childbirth.

Disadvantages of routinely testing all newborn infants may include: infringing a woman's right to privacy and deterring women from accessing labour and delivery services. Counselling women in these circumstances would be

challenging, though essential to enable the mother-infant pair to benefit from safer infant feeding. Concerns about deterring attendance at health facilities need to be addressed. So far, inclusion of opt-out HIV testing for adults has not decreased numbers of people attending services and acceptability of such testing has been shown to be high in several reports.[27-31] While these findings are reassuring, they may not reflect outcomes of routine testing of newborns. Routine testing of newborns has occurred in several states in the USA since 1999. With this policy and opt-out testing for pregnant women, HIV testing coverage is near universal.[32] To our knowledge, no reports of decreased attendance at health facilities have been published.[33]

Essentially, a case could be made that the best interests of the infant and the infant's right to preventive health care (article 24 of CRC)[25] supersede the woman's need for autonomy. Further ethical and legal consideration of this scenario is necessary. It is surprising that paediatricians have not been more vociferous advocates for routine testing of newborns, well within the best interests of those they serve. Similarly, children with AIDS could argue that by failing to test them for HIV exposure, the health providers who cared for them around childbirth neglected to protect them from HIV infection and did not act in their best interests, as legally obliged. That would make a fascinating, perhaps winnable, legal test. Schuklenk and Kleinshmidt go further, arguing for mandatory HIV testing for women who decide to carry the fetus to term.[34] They contend that women who choose to carry a fetus to term and choose not to reduce its chances of contracting HIV constitute harm to others. The authors write: 'choosing deliberately not to act to prevent harm when one could have acted without unreasonably high costs to oneself is comparable to similarly deliberate actions that actively produce the same amount of harm'.

POSTPARTUM PMTCT SERVICES

Patient-provider encounters in child health and immunisation clinics could be used to reduce MTCT. For women who have not accessed HIV testing during pregnancy or around childbirth, identifying HIV infection and supporting safer infant feeding could reduce transmission through breastfeeding, which accounts for a third to half of HIV infections in infants. Postpartum testing may be an important measure while coverage of HIV testing in antenatal clinics is being improved. Also, women who previously declined testing may reconsider their decision or form better rapport with the health worker who offers testing. Women are particularly vulnerable to HIV acquisition during pregnancy and postpartum (for reasons of biology and behaviour, such as lower condom use) and retesting of women who tested negative during pregnancy may identify recent infection. During acute HIV infection, risk of transmission to breastfeeding children[35] and sexual partners is high.

Within child health clinics, postpartum PMTCT services could be built around HIV testing and counselling; infant feeding counselling and support; entry to HIV prevention, care and treatment services; as well as provision of family planning counselling and contraception. Reducing unintended pregnancies among HIV-infected women has been promoted as a key component of PMTCT strategies. Many HIV-infected women have an unmet need for family planning services, especially with shortened lactational amenorrhoea due to replacement feeding or early cessation of breastfeeding. At any time during the breastfeeding period, identifying HIV infection in women or HIV exposure in infants enables them to benefit from infant feeding counselling and support for safer feeding options.

CONCLUSION

In sum, while HIV infection in infants has effectively been eliminated in many settings, in Africa the potential for intervention at each service delivery-point is, so far, underutilised and of low quality. There is an inequitable mismatch between the HIV prevention needs of children and the services provided, necessitating a critical review of prevailing strategies. Despite the level of funding and attention available for HIV interventions, by measures such as coverage, outcomes and equity, PMTCT programmes have performed worse than syphilis control or ART programmes. PMTCT has fallen off the HIV bandwagon and needs to climb back on. For that to occur, stronger bolder national and international leadership is needed, reenergising the current approach with innovative strategies based firmly on public-health principles.

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OPINION

WHY IS HIV PREVALENCE SO SEVERE IN SOUTHERN AFRICA?

The role of multiple concurrent partnerships and lack of male circumcision – implications for AIDS prevention

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A 'Think Tank' meeting on AIDS prevention in the high HIV prevalence countries in southern Africa, convened in Lesotho in May 2006 by SADC and UNAIDS, concluded that 'high levels of multiple and concurrent sexual partnerships by men and women with insufficient consistent, correct condom use, combined with low levels of male circumcision are the key drivers of the epidemic in the sub-region.'[1] The top two 'key priority interventions' recommended by the HIV-AIDS, reproductive health, epidemiological and other experts participating in the Think Tank meeting were: (*i*) 'Significantly reduce multiple and concurrent partnerships for both men and women', and (*ii*) 'Prepare for the potential national roll out of male circumcision ... depending on the outcome of the [now successfully completed] Kenya and Uganda randomized trials'. Various other factors in the region's HIV epidemic, including a range of gender issues, especially the need for greater male involvement in HIV prevention, high prevalence of sexual violence, low HIV risk perception, and pervasiveness of transactional sex among young people, especially young women, were also discussed, and continued promotion of primary abstinence, greater access to HIV counselling and testing and access to condoms, especially in high-risk situations, were also recommended. This paper, however, focuses on the evidence underlying the Prevention Think Tank Meeting's two main conclusions.

The highly generalised HIV epidemic in southern and parts of east Africa is uniquely severe. Elsewhere, HIV transmission continues to be strongly associated with especially high-risk activities, namely use of injectable drugs, male-to-male anal sex, and sex work, and the most effective means of prevention are now generally recognised.[2] Although HIV has been present for nearly two decades in much of Asia, Latin America and eastern Europe, extensive heterosexual spread has seldom occurred in those regions.[3-6] While there is concern over the possibility that it could still occur, for the foreseeable future southern Africa will certainly remain by far the most severely affected region of the global pandemic.[6-9]

Although there has been some decline in HIV in parts of eastern Africa, rates remain extremely high in much of southern Africa.[2,7-9] The overwhelming burden of HIV is still concentrated in this region, home to less than 2% of the global population but at least one-third of all HIV-infected people. Infection rates in adults in South Africa, Swaziland, Botswana and western Kenya range from 20% to 35%, roughly an order of magnitude higher than anywhere else in the world, outside of Africa.[2]

What might account for this pervasive discrepancy? The now conclusive body of epidemiological and biological evidence confirming the strong association between lack of male circumcision and HIV[10-15] is increasingly understood to explain much of the roughly fivefold difference in HIV rates between southern and western Africa[7,16] (Fig. 1). In 2005, a randomised clinical trial of male circumcision for HIV prevention in Orange Farm, South Africa, found that the procedure reduced a man's risk of infection by at least 60%, and two similar clinical studies in Kenya and Uganda were recently halted prematurely, also due to robust findings.[17-19] However, this key driver does not explain why HIV has spread so much more extensively in southern Africa than in India or in Europe, where circumcision is similarly uncommon. Although sexual cultures do vary from region to region,[20] these differences have not been studied in sufficient depth and their significance is not so obvious. For

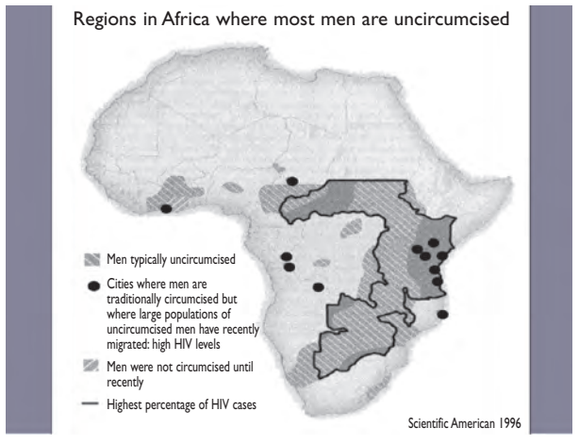


Fig. 1. Male circumcision and HIV in Africa.

example, Demographic and Health Surveys and other studies suggest that, on average, African men typically do not have more sexual partners than men elsewhere.[21] A comparative study of sexual behaviour, conducted by the World Health Organization (WHO) in the 1990s, found that men in Thailand and Rio de Janeiro were more likely to report five or more casual sexual partners in the previous year than were men in Tanzania, Kenya, Lesotho, or Zambia. And very few women in any of these countries reported five or more partners a year.[22,23] Men and women in Africa report roughly similar, if not fewer, numbers of lifetime partners than do heterosexuals in many Western countries.[21,24-26]

Of increasing interest to epidemiologists is the observation that in Africa men and women often have more than one – typically two or perhaps three – concurrent partnerships that can overlap for months or years. For example, according to the WHO study, 18%, 22% and 55% of men in Tanzania, Lusaka (Zambia) and Lesotho, respectively, reported having two or more *regular*, ongoing (lasting at least a year) sexual partnerships in the previous year, compared with only 3% and 2% of men in Thailand and Sri Lanka. Among women, 9%, 11% and 39% in Tanzania, Lusaka and Lesotho reported two or more regular partnerships in the previous year, compared with just 0.2% and 1% of women in Thailand and Sri Lanka[22,23] (Fig. 2). This pattern of concurrent partnerships differs markedly from that of the pattern of serial monogamy more common in the West – i.e. the tendency to have one relatively long-term (a few months or longer) partner after another – or the more 'one-off' casual and commercial sexual encounters that occur everywhere.[23,27,28]

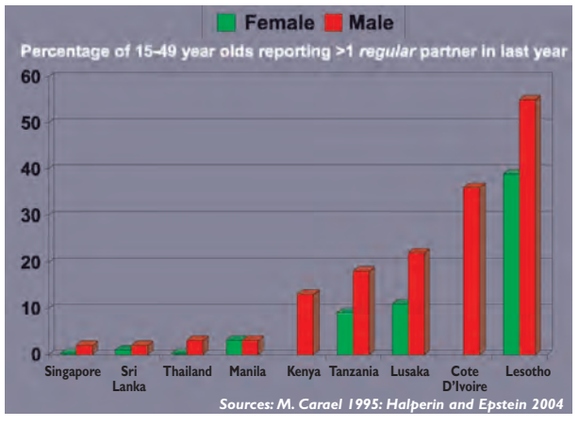


Fig. 2. Concurrent partnerships globally.

Morris and Kretzschmar used mathematical modelling to compare the spread of HIV in two populations, one in which serial monogamy was the norm and one in which long-term concurrency was common.[28] Although the total number of sexual relationships was similar in both populations, HIV transmission was much more rapid with long-term concurrency – and the resulting epidemic was some 10 times greater. The effect that Morris and Kretzschmar measured was due to the impact of sexual networking alone; they assumed that the infectiousness of HIV did not vary over time. However, it is now established that viral load, and thus infectivity,[15] is much higher during the 'acute infection' window period (typically about 3 weeks long) initially following HIV infection.[27,29,30] The combined effects of sexual networking and the acute infection spike in viral load means that as soon as one person in a network of concurrent relationships contracts HIV, everyone else in the network is placed at risk. In Lesotho, for example, according to a national Reproductive Health Survey conducted in 2002, 20% of men and nearly 10% of women reported having two or more partners during the past 4 weeks[31] (Fig. 3). In contrast to this pattern of concurrent partnerships, serial monogamy traps the virus within a single relationship for months or years, so when a new partner is engaged the acute infection period of unusually high HIV infectivity has usually passed.

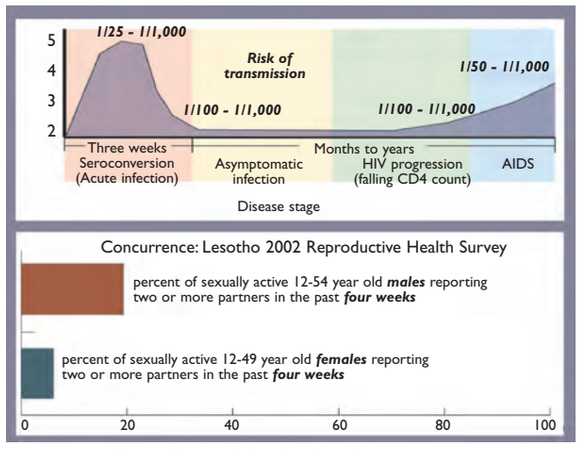


Fig. 3. 'Acute infection' and concurrence.

Morris subsequently studied sexual networks in Uganda, Thailand, and the USA.[28] She found that Ugandan men reported fewer lifetime sexual partners than Thai men, but while the Thais mainly had one-off encounters with sex workers, the Ugandan men's relationships tended to be of much longer duration. Given that the per-act probability of heterosexual HIV transmission is, on average, very low,[15] the much higher number of cumulative sexual acts – and hence the likelihood of transmission – within any given relationship was much greater in Uganda than in Thailand or the USA. In addition, except for sex workers, very few Asian women have concurrent partners, whereas a larger proportion of African women do. Even though the Ugandan women in Morris's study reported fewer concurrent relationships than Ugandan men, the multiple partnerships that some of them did have helped importantly to maintain the extensive interlocking sexual networks which facilitate the generalised spread of HIV.[23,28]

Although most African women in concurrent partnerships are not sex workers, such relationships often include a powerful element of sexual-economic exchange, related to issues of gender and income inequality, sexual culture, poverty, and the globalisation of consumerism.[32,33] A recent study from Malawi found that among some 1 000 adult villagers, whose sexual relationships were carefully mapped by researchers over a 2-year period, some 65% were 'connected up' in the same sexual network[34] (Fig. 4). Unfortunately the investigators did not inquire whether the sexual relationships were of a concurrent

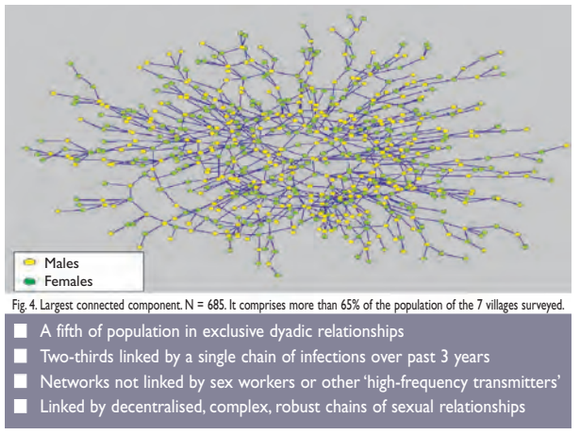


Fig. 4. Sexual networking in Likoma, Malawi.

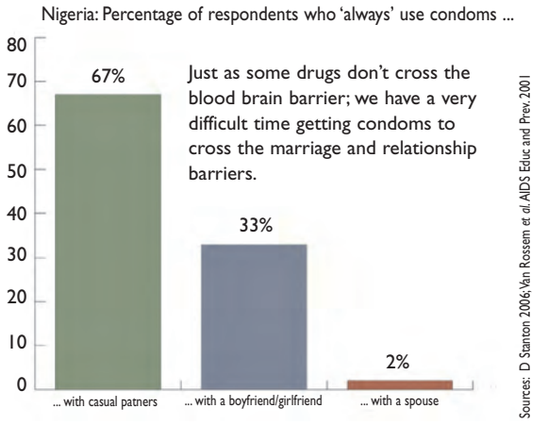


Fig. 5. Condom use in longer versus shorter-term relationships.

or serial nature, although data from similar populations in southern Africa suggest the likelihood that concurrency also plays a key role in that Malawi population.[1,2]

Although polygamy, and therefore a type of concurrency, is common in much of north and west Africa, as well as in other Muslim regions of the world, HIV infection rates tend to be considerably lower there. The most likely explanation is twofold: first, in most of west Africa and in all Muslim countries, nearly all men are circumcised.[5,6,9,13] Secondly, large-scale heterosexual concurrency networks can only emerge if a significant proportion of women are also engaging in multiple, longer-term relationships. But in Muslim societies generally, women's sexual behaviour tends to be under strict surveillance, which limits the extent of sexual networks.

Such differing patterns of sexual behaviour and the resulting differences in sexual networks have important implications for HIV prevention programmes and outcomes. Consistent use of condoms has been effectively promoted in Asia's organised brothels, most notably in Thailand and Cambodia, as well as, for example, in the Sonagachi project in Calcutta,[35] and among sex workers in the Dominican Republic, Abidjan, Senegal, Harare and elsewhere.[36-38] Yet, from the gay communities of Australia and San Francisco to the market towns of Uganda, it has proved much more challenging for people in ongoing longer-term relationships to consistently use condoms[37-43] (Fig. 5). In southern Africa – unlike in most of Asia or Latin America – such longer-term relationships are often the ones in which HIV transmission takes place. For years, condom promotion has been a mainstay of donor-funded HIV prevention in Africa, yet a comprehensive review commissioned by UNAIDS concluded that, although condoms are highly effective when used correctly and consistently, 'no clear examples have emerged yet of a country that has turned back a generalized epidemic primarily by means of condom promotion.'[37]

Furthermore, a large experts' meeting convened by WHO in July 2006 concluded that, although treatment of sexually transmitted (bacterial) diseases continues to be an important public health measure, the impact on preventing HIV transmission, especially in high HIV prevalence, more generalised epidemics, is likely to be fairly minimal[31] (WHO Report forthcoming). And perhaps even more sobering, several meta-analyses and other rigorous reviews of the data on the impact of HIV testing and counselling on preventing HIV infection, particularly in Africa, so far tend to similarly suggest the likelihood of limited impact (especially for individuals who test HIV negative), although access to testing is clearly very important for various other reasons, including as an entry point for care and treatment.[44-46]

Thus while condoms (and STI treatment and HIV testing) remain important interventions, there is considerable evidence that people worldwide are more likely to use condoms during commercial and casual sexual encounters than in longer-term relationships, in which there is a sense of commitment and trust.[1,37-40,42,43] Also, because HIV can spread so efficiently through populations in which concurrent partnerships are common, everyone's risk is thereby increased, including persons who are commencing a sexual relationship, those who are monogamous with a partner who is not, or people who practise 'serial monogamy'. It is hoped that wider understanding of the dangers of longer-term concurrency could lead to a shift in social norms emerging from a deeper appreciation of the importance of avoiding and addressing concurrency, not only for those whose behaviour is 'risky' according to conventional standards, but also for those whose behaviour is not considered risky, such as monogamous women.

Although clearly no simple solution exists to this complex problem, it appears imperative that in addition to condom availability and other prevention approaches in Africa, there needs to be franker discussion and concerted public-health efforts addressing the dangers of having more than one longer-term sexual partner at a time, or of having a partner who has more than one longer-term partner. Because most Africans do not have high numbers of partners, they may not realise the special dangers of having long-term concurrent partners, especially in regions of high HIV prevalence. In much of southern Africa, even people with only two lifetime partners – hardly high-risk behaviour by Western standards – need to appreciate just how risky that one extra partner can be, for themselves and others, if the relationships are long-term and concurrent.

At a SADC/UNAIDS-organised regional consultation on social change communication for HIV prevention, held in Swaziland in October 2006, it was concluded that the focus of communications programmes across the region over the next 5 years should be on partner limitation.[47] Because in many African countries cultural practices and traditional policies allow and sometimes even encourage multiple partnerships for men, communications programmers will need to work closely with local leaders in order to get the messages right.

In addition, it was agreed that expanded and improved male circumcision services will need to be placed within a broader framework of male reproductive and sexual health.[1,47] Future communications programming will also need to emphasise that while male circumcision is protective, it certainly is not fully protective. Therefore messages which combine information about male circumcision along with promotion of partner limitation and consistent condom use will be essential.

It may seem simplistic to expect people to change their sexual behaviour, once they learn how dangerous it is to have multiple concurrent partnerships in areas of high HIV prevalence. There are, after all, numerous social, cultural and economic reasons why multiple concurrent partnerships exist. In many societies, having multiple partners is a powerful signifier of masculinity, and a relatively wealthy man may even be expected to have more than one wife or girlfriend as long as he can afford to do so.[48] It is also the case that many women in Africa – especially poor women – may be compelled to rely on multiple partners for support, and often have little power to negotiate with their partners about the timing of sex, use of condoms, etc. A detailed exploration of sexual culture in southern Africa is beyond the scope of this paper, but any HIV prevention strategy to address partner reduction and faithfulness should also take place within a wider campaign to address gender issues and to raise the status of women generally.[49]

Despite such important limitations, there is evidence that focused, clearly articulated partner reduction campaigns can make a difference, even in countries where traditional norms would seem to militate against behaviour change. The 'Zero Grazing' (partner reduction and faithfulness) campaign in Uganda,[31,33,37,39,50-53] coupled with evidence from other places such as Kenya and Addis Ababa,[54,55] suggests that fundamental society-wide changes in sexual norms and resulting declines in HIV rates can occur in Africa, just as they did in highly affected communities in north America and Europe in the 1980s.[56,57] Large surveys conducted in Uganda by WHO/the Global Programme on AIDS indicate that between 1989 and 1995 there was a 60% decline in the percentage of people reporting two or more sexual partners in the past 12 months.[41,50] The proportion of men reporting three or more partners fell even more dramatically[41,51] (Fig. 6).

These behavioural changes are believed to explain much of the decline in HIV *prevalence* that occurred during the 1990s, which modelling studies suggest was preceded by a steep decline in *incidence* – or the rate of new infections – during

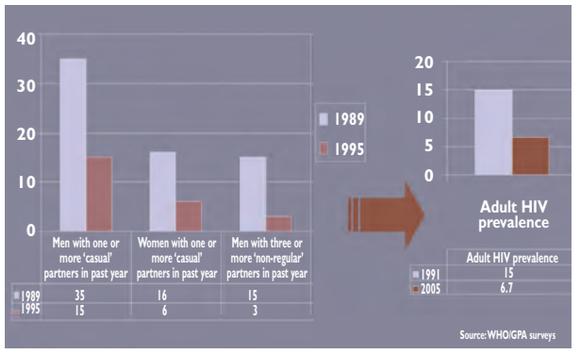


Fig. 6. Behavioural and HIV trends in Uganda.

the late 1980s, when the Zero Grazing campaigns were at their height.[8,50-53] A sampling of newspaper articles on HIV-AIDS in Kampala's main English language paper, *The New Vision*, between 1987 and 1992 found that of 20 articles in the period 1987-1989, 12 mainly addressed behaviour change (partner reduction-related issues in particular), whereas of 25 articles from 1990 to 1992, only 2 did so (although several in the latter period addressed issues such as increasing the condom supply). For example, a long piece on 'zero grazing' and other 'B' types of behaviour change, titled 'Slim [AIDS] is forcing people to change social habits', from 23 October 1987, contained this anecdote: 'In Bugolobi, a young housewife with three children declared, with a gleam in her eye, "My husband stays at home much more. And I encourage him to do so by enthusiastically keeping him informed of the latest gossip about Slim victims."'[51] An 11 November 1989 editorial in *The New Vision* concluded, 'AIDS has no cure. Protect yourself by zero-grazing.'

Recently, attention has been drawn to the reversal of the prevention success in Uganda, where there are some indications that HIV prevalence has increased.[2] This has been variously attributed to temporary shortages of condoms, or the expansion of abstinence-until-marriage programmes conducted by evangelical churches that may promote unrealistic standards of sexual behaviour.[58,59] However, the stagnant and worsening trends in Uganda date from about 2000, significantly before either the condom shortages or the proliferation of such abstinence-only programmes. Another possibility is that these negative HIV trends are due, at least in part, to the phasing out of the 'Zero Grazing' and other partner reduction/fidelity-focused campaigns of the late 1980s.[60,61] Indeed, Demographic and Health Surveys conducted between 1995 and 2005 suggest that there has been a considerable increase in the number of sexually active adults reporting multiple partners. The recognition that partner reduction has been neglected in Uganda's more recent prevention programmes, and that it must be a central theme of future campaigns, was emphasised in the final recommendations of a 3-day research symposium, organised by Makerere and Harvard universities, which was held in Kampala in December 2006.[62]

The Ugandan case is not unique. In Kenya, where HIV prevalence has also declined considerably, albeit more recently,[2] the percentage of men reporting two or more sexual

partners in the last year fell very sharply, according to Demographic and Health Surveys conducted between 1993 and 2003.[31,38] A study in rural Zimbabwe found an approximately 50% decrease in the percentage of men reporting a new sexual partner in the last month over a roughly 3-year period, coinciding with a significant decline in HIV prevalence and incidence[63] (Fig. 7). In Swaziland, where the government recently began aggressively promoting messages such as 'I Choose to Have Only One Sexual Partner' and 'Your Secret Lover Can Kill You', preliminary data from large surveys conducted in 2005 and 2006 found that after only 1 year, the percentage of adults reporting two or more partners in the last 4 weeks had fallen by approximately half.[64-66] This 4-week indicator roughly covers the 'acute infection' period, also approximately 3 - 4 weeks, and so may provide some measure of the degree of sexual networking in the population and the potential for highly efficient transmission of HIV.

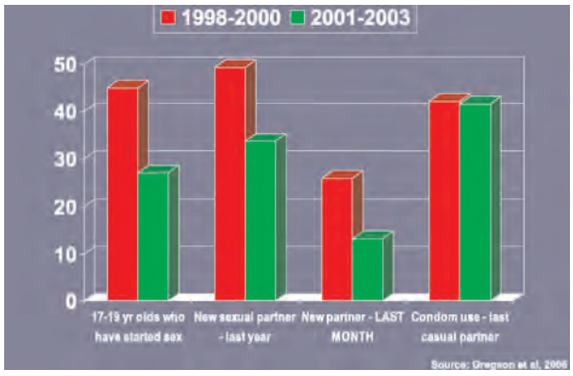
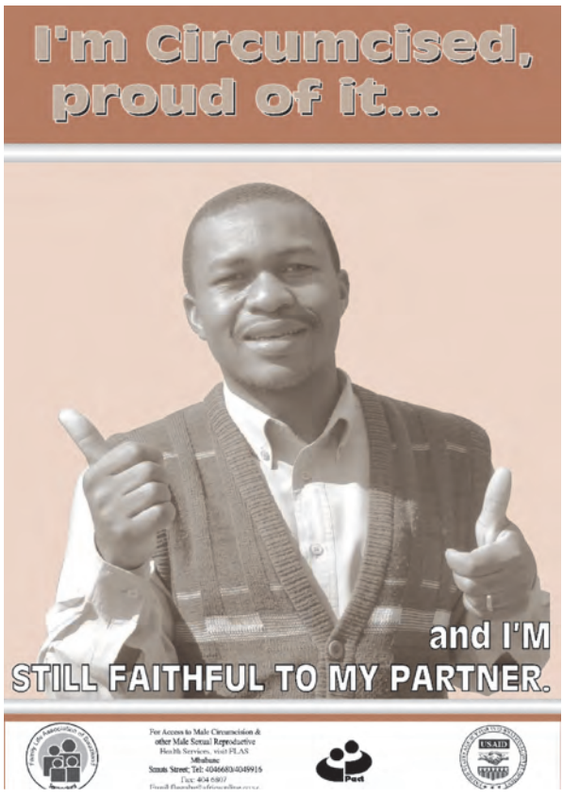


Fig. 7. Behaviour change among males in Manicaland, Zimbabwe.



In conclusion, although partner reduction/faithfulness approaches have received relatively little attention in most of Africa,[67] they appear to be feasible and epidemiologically crucial. The experiences of Uganda and some other places, where campaigns emphasising 'B' appear to have been associated with population-wide declines in HIV,[31,33,38,39,41,50-53] suggest there is empirical validity to the common-sense notion of emphasising partner limitation – in addition to other crucial approaches, such as the promotion of consistent condom use and increased access to safe and affordable voluntary male circumcision – for HIV prevention.

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2007 CLINICAL GUIDELINES ON ANTIRETROVIRAL THERAPY MANAGEMENT FOR DISPLACED POPULATIONS

1. PREAMBLE

Providing HIV-related services to displaced populations is a difficult yet critical undertaking, which is firmly rooted in international human rights law. Protection offered under this law and, in particular, article 12 of the International Covenant on Economic, Social and Cultural Rights, confirms '*the right of everyone to the enjoyment of the highest attainable standard of physical and mental health*'. This right requires health workers to take steps that are necessary for '*the creation of conditions which would assure to all medical service and medical attention in the event of sickness*'.[1]

In addition, health workers who treat displaced persons are guided by the same principles that govern the treatment of any patient, irrespective of nationality or ethnic origin, which include an intrinsic respect for human life and an oath to act in the patient's best interest when providing medical care.

Nonetheless, displaced persons are a unique group with special needs. They are often stigmatised, marginalised and discriminated against, making them highly vulnerable and insecure in their host country. Those in need of treatment are often denied care. However, since the rollout of affordable antiretroviral therapy (ART) worldwide, there has been an international push to recognise every individual's right to treatment and to ensure universal access to ART. Displaced persons often come from communities that are least likely to have access to ART, and health workers will be following international law and practice by providing treatment to them.

For those who are already on treatment, health workers often need guidance regarding complications that may arise due to differences in regimens or, if initiated in the host country, due to different conditions the individual may face at the site they will be going to. The management of ART in displaced populations requires health workers to make strategic choices regarding the best care for the individual who may be further displaced. These guidelines outline key principles to guide the health worker in making these sometimes complex choices.

SCOPE OF APPLICATION

This policy is intended to offer guidance to clinicians, non-governmental organisations (NGOs) and governments on the provision of ART among displaced populations, including prevention of mother-to-child transmission (PMTCT), post-exposure prophylaxis (PEP) and long-term ART. These guidelines are not meant to replace national guidelines but to provide additional guidance to health workers to deal with the specific needs of these populations.

As with all HIV and AIDS policies and programmes, ART must be linked to prevention, care and support programmes. ART should not be implemented as a parallel intervention but rather as part of an integrated programme that is in itself linked to other existing services (e.g. reproductive health, nutrition, education and social services).

The guidance set out in this document applies to all displaced populations, including refugees, asylum seekers, internally displaced persons and migrants. Specific guidance is necessary not only because of the unique characteristics of these populations, but also because of their specific vulnerabilities and frequent exclusion from HIV- and AIDS-related services. It is widely recognised that the failure to provide HIV prevention and care to displaced persons not only undermines effective HIV prevention and care efforts, but also undermines effective HIV prevention and care for host country populations.

2. BACKGROUND

Southern Africa is host to approximately 300 000 refugees and asylum seekers, the majority of whom are hosted in South Africa and Zambia. Most refugees and asylum seekers are currently coming from countries with lower HIV prevalence, such as the Democratic Republic of the Congo (DRC), and moving to countries with higher HIV prevalence, such as South Africa. Their vulnerability to HIV infection therefore increases upon arrival. In general, they also come from areas where access to ART is limited.

> '*They see refugees as a threat, as competing for their jobs and women. Nobody sees them as a victim of circumstances.*'
>
> Refugee in Johannesburg referring to local services

The number of migrants in the region is difficult to estimate accurately, as there are no official mechanisms for recording these figures. However, every country in southern Africa is affected by migration, either as a source or destination country.

DEFINITIONS

- **Refugee:** *a person who flees his/her own country because of race, religion, nationality, membership of a particular social group, political opinion or civil unrest/war, and who cannot return home for fear of persecution.*
- **Asylum seeker:** *a person who has applied for asylum and is awaiting a decision on his/her case.*
- **Internally displaced person:** *person who has been forced to flee his/her home suddenly or unexpectedly due to armed conflict, internal strife, systematic violations of human rights or natural disasters, and who is still within the territory of his/her country.*
- **Economic migrant:** *person who moves to another country seeking economic opportunities.*
- **Undocumented migrant** *(often negatively referred to as 'illegal immigrant'): person who has entered another country and remains without the required legal documentation.*

3. RESPONSIBILITY OF THE HEALTH WORKER

It is the role of health workers to act, within a legal framework, as advocates for access to health care, and not to restrict or ration care. The ethical duty of a health worker is to treat patients in a manner that serves the patient's best interest.

Medical assistance should ensure the 'right of everyone to the enjoyment of the highest attainable standard of physical and mental health'[2] and must be offered without discrimination. People in need of health care should not be denied HIV care because of their nationality.

4. MEDICAL MANAGEMENT

All people, including displaced persons, should be encouraged to test for HIV regularly.

Retesting for HIV should occur in all patients who report being HIV positive. This must be done with their informed consent. Counselling should be made available if results from re-testing are negative and confirmatory testing/expert consultation sought.

As is the case with the general population, people from displaced communities may present late with AIDS-defining illnesses, as well as for PEP and antenatal care. Advanced presentation is *not* a reason to deny care. Earlier diagnosis should be pursued at every opportunity.

Mythbusters

'Conflict always increases HIV'

On the contrary, despite the sexual violence, trauma and breakdown of family and community structures, evidence suggests that there are 'protective' factors in a refugee setting that may offset these risks. Furthermore, displaced persons often come from countries of origin with lower HIV prevalence and move to countries of asylum with higher HIV prevalence.[3] Thus, these populations often have lower HIV prevalence than their surrounding host communities, particularly in southern Africa.[4]

'Displaced persons engage in high risk behaviour'

While displaced persons are vulnerable to exploitation and abuse, they have often benefited from the assistance of international organisations. For example, dedicated HIV awareness programmes and training in many refugee camps have resulted in a high level of skills and knowledge with less risky behaviour. Displaced people can use this knowledge in their country of asylum as well as upon return to their home country.[5]

'High mobility among displaced persons prohibits good adherence'

Displaced persons are often denied access to care because of fear that they are too mobile. However, by the end of 2003, refugee populations remained on average in their host country for 17 years.[6] Even within a country, they are far less mobile than many assume and may move around less than local clients who work far from home.[5]

'Providing care will bring on a flood across the border'

As HIV- and AIDS-related care is made increasingly available in the region and as more people can access such services, the more they tend to stay where they are. In countries that have provided free ART to refugees, there has not been an increase in movement across borders.

'Displaced persons never have support structures'

There are often tight and extensive support networks of similarly affected people within the host community; these may, however, not involve family, friends or more traditional support networks. Often innovative ways of ensuring adherence to ART, such as using clinical staff, counsellors and support groups, have proven effective.

'Conflict is limited to a short period'

Unfortunately, most conflict lasts for years and even decades, resulting in conditions that force displaced people to remain in their host countries for extended periods.

Displaced persons may be anxious that disclosure of their HIV status will have implications for their residency, resettlement and other legal consequences. The reality is that HIV status does not have an impact on the legal status of a displaced person in the southern African region.

Despite this, displaced persons may be anxious about disclosing their HIV status. Some refugees may wish to remain anonymous for a myriad of reasons, including very real security concerns. It is up to the health worker to deliver care in a manner that does not put them or their families in danger. Health workers must reassure patients that their privacy and confidentiality in this regard will be respected.

A full history, clinical, psychosocial and available laboratory evaluation should be done for all patients according to the national protocol.

4.1 ANTIRETROVIRAL THERAPY (ART)

ART is a life-saving intervention.

In principle, ART should be lifelong and sustainability should therefore be key. However, even if sustainability is not guaranteed or is uncertain, immune reconstitution on ART, even for short periods, can yield significant clinical benefits. Furthermore, provision of ART is rapidly evolving in the region, and is increasingly accessible even in very poorly resourced areas. Hence, starting someone on ART for even a limited period of time may allow them to access more sustainable treatment at a later stage. However, there is substantial evidence that ART interruptions may be harmful, and this option must be carefully weighed and generally only considered in severe disease.

> '*From what I have seen, compliance among foreigners is good, better than South African citizens.*'
>
> South African doctor

Adherence support needs of displaced persons may be very different from those of the local community. A displaced person may not have the traditional support of family or friends, although there may be strong cohesion among displaced communities who share similar reasons for displacement. As the circumstances of displaced persons often change without warning, assistance needs should be constantly assessed, and appropriate counselling and support provided where necessary.

4.1.1 Initiation criteria for patients with no ART history

Patient preparedness

Patients must make an informed decision to begin and be adherent to ART and, as with other patients, proper counselling is key to ensuring the displaced person's understanding of these principles. Counselling in an appropriate language and with due regard for cultural differences is crucial. UNHCR has translation resources available for refugees.

Counselling should also take into consideration the particular background and human rights context of the displaced person. The possibility of treatment interruptions should they be further displaced must be specifically addressed during counselling, e.g. if they travel to a different area, they may need to find an alternative drug supply and HIV care network. The possibility of interruption should not be used by the health worker as a reason to deny access to care. Instead, strategies should be explored with the displaced person to find solutions.

In the event of informed refusal of ART, as with any other patient, continued counselling is required. Furthermore, access to other interventions including prophylaxis and treatment of opportunistic infections should not be withheld.

Country-specific exclusion criteria for ART

These criteria should be viewed very critically, taking into consideration the specific circumstances of displaced persons. Certain criteria may need to be modified to include displaced persons in ART programmes. For example, some programmes ask for a 'treatment buddy', which can be a challenge for displaced persons who are often alone or separated from traditional support structures. Imaginative solutions are usually available and should be explored (see 'Solutions' box).

Biological criteria for initiation of ART

National guidelines should be adhered to, where these are available. Where there are no national guidelines, World Health Organization (WHO) guidelines should be followed.

The absence of laboratory facilities should *not* be used to exclude HIV-infected people from treatment. For example, if a displaced person does not have access to or cannot afford CD4 testing at initiation, WHO guidelines clearly state that clinical staging is an acceptable indicator for ART initiation.

If return to country of origin or further movement is imminent

The following considerations should govern the decision to commence ART immediately:

i. ART is a lifesaving treatment and should be carefully evaluated in each case, regardless of whether return or further displacement is imminent.
ii. In many cases, the conditions and access to ART at the site being travelled to are unknown. Information may be out of date in many cases, especially as ART access has expanded so rapidly. Conflict may interrupt access to previously accessible health services. Displaced persons may therefore return to HIV care systems that may be either stronger or weaker than they, or the assessing health worker, anticipated.
iii. Stage of disease and anticipated availability of treatment at the site being travelled to should guide the urgency of initiation.

iv. If patients have advanced clinical disease (severe AIDS-defining disease or a low CD4 count (< 50 cells/μl)), they should be advised to delay their departure and ART commenced immediately. However, clinical discretion is required in all cases.

v. If the patient is WHO stage 3 or healthy, with a good CD4 count (if available) and

- **Treatment is available at the site being travelled to:** The site of initiation (either at the current health site, or at the site being travelled to) should be determined by the following factors: timing of departure, duration of travel, ART regimen at the receiving site (if known), anticipated side-effects and conditions on arrival (e.g. local waiting time to access ART). All these need to be discussed with the patient so an informed decision can be made.
- **Treatment is NOT available at the site being travelled to:** The displaced person should be encouraged to remain where they are and initiate ART for at least 3 months to monitor potential side-effects and adherence, and subsequently be provided with a stock of medication for 3 - 6 months if possible.
- **The individual insists on leaving immediately or in the near future:** These individuals must receive comprehensive advice on options available (see below). All should be considered sub-optimal.

  Options include:

  a) leaving with no ART

  b) initiation for a short period prior to leaving together with additional ART stock

  c) leaving with a supply to be initiated at the site being travelled to (with referral letters and extensive pre-adherence counselling).

  The guidelines group felt that options (b) and (c) were dangerous, and should only be considered in exceptional circumstances.

  In many situations, the person will be going to an area with poor or limited health care, limited or no access to clean water or accommodation and food insecurity. In this situation, option (a) may be more appropriate.

  For other individuals who are going to better conditions and have a good understanding of HIV and ART, options (b) and (c) may be considered if this is the only option. Consequences of initiating ART in the (b) and (c) scenarios may include developing side-effects in an unsupported environment, possible development of ART resistance due to the lack of adherence support, and the difficulties of initiating and maintaining treatment during a stressful and unstructured time. These consequences must be fully explained to the patient.

vi. There may be additional reasons for delaying treatment initiation, other than those listed above, such as patient readiness, practical considerations (such as side-effects during travel and reintegration), concurrent medical conditions that may worsen on ART (e.g. immune reconstitution diseases may present catastrophically and the receiving site may not have the resources to manage them), and other considerations. The risks and benefits of deferring treatment must be carefully weighed against immediate initiation; options should be discussed with the patient, including delaying departure.

vii. This decision-making may require significant ART expertise, and the health worker should consult if not confident that s/he has the expertise to give adequate counsel.

viii. Choice of regimen. In general, try to match the regimen to the one the individual is most likely to be on over the next year. If return or displacement is likely to be soon, try wherever possible to match the regimen to that available in the area the person is going to.

Solutions to problems encountered when initiating patients on ART

Problems	Solutions
CD4 count is unavailable or unaffordable	■ WHO clinical staging is simple, and relatively sensitive and specific.
Treatment buddy is required by national guidelines	■ Use a friend, companion, family member, support group, local health worker, or local faith-based or non-governmental organisation (NGO) member.
No counsellor is available who speaks the language	■ Contact UNHCR for list of translators.
Payment, lab costs, transport costs are an obstacle	■ Displaced persons must be assisted with a waiver process if one exists; others can be referred to NGOs and social welfare organisations, which are also resources in many areas. Refugees can be referred to UNHCR.
Geographical exclusion criteria exist, but patient is unable to return to home site	■ If outside treatment catchment area, patient must demonstrate ability to regularly attend appointments and then assisted to negotiate for inclusion with the relevant authorities.

4.1.2 Patient presents on ART or with history of previously taking ART

In circumstances where the displaced person is either currently on ART, or has a history of previously being on ART, the following is recommended:

- A repeat HIV test to confirm their infection.
- If the individual is currently on ART, continue treatment with no interruption.

- If possible, a viral load and CD4 count should be done at the time of the first visit. If the viral load is raised adherence intensification is usually warranted. Expert opinion should be sought before ordering resistance testing, if available.
- If there has been a treatment interruption, try to restart treatment as soon as possible, after careful assessment of the reasons for the interruption (see below). The viral load may be high if the interruption is significant.
- Adherence counselling and support should be undertaken in light of the new circumstances.

Choice of regimen if currently on ART

In general, most patients in sub-Saharan Africa are currently initiated on d4T or AZT, 3TC and a non-nucleoside reverse transcriptase inhibitor (NNRTI), either nevirapine or efavirenz.

- **If on same regimen as national programme:** Continue same regimen.
- **If on different regimen from national programme:** If the national guideline supports the different regimen, continue with this regimen and initiate monitoring according to the local algorithm. Occasionally, the national regimen protocols may offer better treatment options, or new treatment options may become available, and these cases should be assessed with suitable expertise.

  If the national guideline does not support the regimen, the following possibilities should be considered, as they may not allow patients to go on to the regimen indicated under the national protocol:

  - history of side-effects and co-morbidities
  - history of possible virological, immunological or clinical failure
  - use of concomitant medication.

  In this case, select the best available regimen from available drugs.
- **If on unknown regimen, with minimal history:** In general, these patients should be initiated on the national guideline's first-line therapy, and followed closely. Where possible, a viral load after 6 weeks of treatment should be used to indicate efficacy and a significant drop in viral load (1-log) should be anticipated if the regimen remains effective.

Choice of regimen if ART was interrupted

Establish the cause of the interruption. Note that displaced persons are at greater likelihood of treatment interruption due to factors beyond their control, e.g. conflict resulting in displacement from their normal ART site.

'They saved my life.'

Migrant in Johannesburg on ART through faith-based organisation

Routine evaluation:

- If adherence is an issue, this needs to be explored. However, there is no evidence that displaced persons are less adherent than local populations.
- If virological failure was the reason, treat as per national protocols, which may mean accessing second-line regimens, if available.
- If due to side-effects, subsequent drug choices should be carefully evaluated.
- If interruption was due to drug supply issues, and there were no adherence, resistance or toxicity issues, ART should be reinitiated as soon as possible.
- If the previous regimen was the same as the national programme, restart ART. Nevirapine deserves special consideration in the event of the patient having a high CD4 count, as it is associated with significantly increased toxicity. If nevirapine is restarted after an interruption of > 1 week, recommence with the 2 week lead-in dose, and monitor alanine transaminase closely for the first 3 months of treatment, if laboratory monitoring is available.

If the previous regimen is different from the current recommended regimen, considerations should be as above.

4.1.3 Contingency planning

Displaced persons can be affected by unforeseen events, causing them to move unexpectedly. This needs to be explored at every visit.

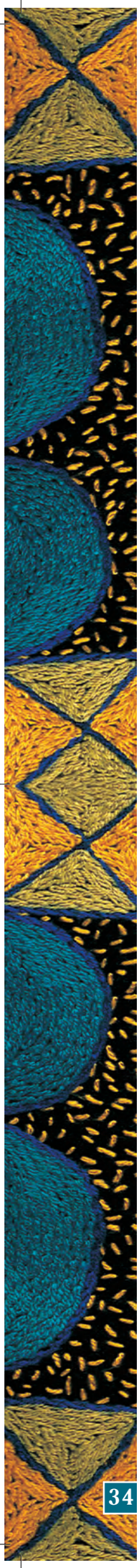
Discuss the provision of a personal ART stock where assessed to be necessary (2 - 4 weeks will allow for time to make alternative plans for ART access).

All patients should have a clinical HIV summary, such as a treatment card, which includes their drug regimens, prior toxicity, illness history and laboratory results. All patients should also be aware of their basic medical history and be able to relate it verbally. This assists continuity of treatment in the event of unplanned displacement.

If on a non-nucleoside reverse transcriptase inhibitor (NNRTI) regimen (which have a long half-life) and treatment is stopped with no possibility of immediate restocking of drugs, consider 'covering the tail' (the long half-life of NNRTIs) by continuing dual nucleosides for a week after stopping the NNRTI, to prevent possible NNRTI resistance.

In the event of unplanned displacement, patients should be cautioned on non-reputable sources of treatment, including counterfeit drugs, cheaper but less effective regimens (such as dual therapy), inconsistent sources of drugs, and poorly trained health worker advice. They should be counselled to seek continued care only through a public or reputable programme.

Sharing of ART and dose reduction/interruption to extend the stock lifespan must be discouraged.



Mythbusters

'Resistance to ARVs is caused by suddenly stopping ART'

Stopping ART suddenly is rarely associated with resistance; poor dosing, poor drug quality and poor adherence are far more common causes. There is concern about stopping NNRTIs along with other classes of drugs, as they have a long half-life. This is discussed above.

'Access to monitoring is poor and hence ART should not be started'

If laboratory monitoring is not available, clinical monitoring, although sub-optimal, is sufficient to start ART.

'Access to guaranteed lifelong therapy is a reason not to start ART'

Treatment may allow a person to live long enough to access more sustainable sources of ART, especially as broader availability increases throughout the region. However, there are dangers in interrupting treatment, and this must be avoided wherever possible.

4.1.4 ART-specific challenges

The choice of ART should take the following into account:

- National guidelines should be used. Within this, try to match this regimen to the possible regimen in the area being travelled to, if travel is anticipated soon.
- Some ARVs (e.g. ritonavir) require refrigeration. Assess availability of refrigeration during travel and at the site they are travelling to and adapt ART accordingly.
- Some ARVs require food intake for optimal absorption. Many regimens require twice-daily dosing. Displaced persons may not have sufficient food available and should be told to take their medications despite lack of food, and warned of possible increased gastrointestinal side-effects. At the same time, food aid should be sought for these persons.
- In many cases, patients may be on fixed-dose combinations (FDCs) in their prior ART site, and this may mean a higher pill burden in their new site if the FDC is not available. The changes should be carefully explained during adherence counselling.
- If the ART choice requires more frequent monitoring, consider the ease and cost of access to the displaced person. As with local populations, transport costs are often a barrier to regular visits.

'People are surprised to see me looking so well. Before they were advising me to save my mealiemeal for my funeral.'

Namibian refugee in Botswana, on ART through a faith-based organisation

- ARVs requiring reconstitution (some paediatric formulations) depend on access to clean water, which may not be easily available to displaced persons.
- The absence of access to laboratory monitoring (either due to lack of facilities or cost) in the current site or site being travelled to should not be used to exclude people from ART. Minimum standards for laboratory monitoring are outlined in the WHO and national guidelines, and should be adapted as much as possible to enable access. If the ART choice requires more frequent monitoring, consider ease and cost of access. For example, a nevirapine regimen should ideally have liver function monitoring in the initiation phase, which may increase the frequency and cost of visits. However, in many cases, nevirapine is the only NNRTI available, and no liver function testing is available, in which case the drug should be initiated with extensive patient counselling.

4.1.5 Management of children

Initiation of treatment should be based on national guidelines. In certain cases, if diagnostic and monitoring facilities are not available, refer to the WHO guidelines for HIV diagnosis that are based on a positive HIV antibody test and clinical findings.

Syrup formulations have large volumes, and can be difficult to carry and refrigerate. This may be particularly relevant to those travelling long distances and should be taken into consideration when making clinical decisions.

In children < 18 months who are diagnosed clinically, parents should be counselled to seek confirmatory testing after 18 months of age with conventional antibody tests. This is particularly important where further displacement is possible.

Unaccompanied minors are a special issue, and may need to follow a special legal process or agreed upon guardian/caregiver arrangements. These need to be expedited as quickly as possible, so as not to delay ART. For refugee children, contact UNHCR for assistance.

4.1.6 Post-exposure prophylaxis (PEP)

In populations affected by conflict, gender-based violence and assault is common throughout the cycle of displacement. Sexual exploitation is also common among female migrants, who can be victims of trafficking. PEP should be considered for displaced persons in need; however, assessment often takes place after the efficacy of PEP has passed. PEP includes HIV, sexually transmitted disease and pregnancy prevention. Trauma and adherence counselling is essential in all cases.

National and WHO/UNHCR[7] PEP guidelines should be followed. If national guidelines exclude displaced persons, treatment should be accessed wherever possible (e.g. from rape crisis centres, NGOs, faith-based organisations, private practitioners). For refugees who cannot access PEP through a local service, contact UNHCR urgently.

4.1.7 Prevention of mother-to-child transmission (PMTCT)

PMTCT services may not be available in the prior site, and hence women may not have been counselled regarding PMTCT. Pregnant women may require counselling on testing, treatment and feeding options available in the host health care environment.

In cases of moving to sites with unknown or poor access to care, similar to treatment for tuberculosis in pregnancy, the pregnant woman and her family should be advised to delay moving until after delivery in order to complete the PMTCT programme.

In cases of moving to sites with established PMTCT programmes, the patient should be advised to immediately seek out local PMTCT programmes on arrival. However, due consideration to the stage of pregnancy, duration/mode of travel and conditions on arrival must be discussed.

A clear referral letter is important at all times, in both the antenatal and postnatal period.

Provision of PMTCT drugs to pregnant women about to move should be considered in case labour occurs during travel or the woman arrives in an area where there is no PMTCT programme. Take note of the considerations described in the section that deals with individuals in need of ART who are facing imminent departure (see section 4.1.1, 'If return to country of origin or further movement is imminent') to counsel appropriately.

4.2 NON-ART CONSIDERATIONS

4.2.1 Tuberculosis (TB) treatment, and primary and secondary prophylaxis for opportunistic infections including co-trimoxazole, fluconazole and isoniazid

National guidelines should be followed. Interruption of prophylaxis should be avoided through rapid referral to local sites providing these drugs. People with TB should be encouraged to complete TB treatment before further movement.

Co-trimoxazole demonstrates significant benefit in areas affected by malaria and bacterial infections, as well as in people with WHO stage 2, 3 and 4 disease. Co-trimoxazole should be strongly considered, in line with national and WHO guidelines.

A contingency stock of prophylactic medications, as for ART, is recommended for people at risk of unplanned movement (2 - 4 weeks supply, like ART).

4.2.2 Other illnesses

Malaria is extremely common in the region, but typhoid, trypanosomiasis, viral hepatitis, cholera, amoebiasis, measles and other diseases that can affect travellers should be considered, and appropriate prevention advice given.

Be aware of other countries' endemic AIDS-defining diseases that may not be common in the host country (e.g. kala-azar in Somalia, histoplasmosis in Zimbabwe).

4.2.3 Language

Using family members or community members as interpreters carries risks regarding respect for confidentiality and inappropriate disclosure, and should be avoided where possible. Furthermore, information may be less forthcoming through a third party if the party is known to the person. All efforts should be made to have an independent interpreter who has been trained in issues of confidentiality.

Ongoing adherence counselling is a challenge if no ready interpreter is readily available.

For refugees, do not refer them to their country's embassy, as that may jeopardise their asylum status. This may however be an option for other displaced persons, e.g. economic migrants.

For help with refugees, contact UNHCR, who may be able to identify suitable interpreters.

4.2.4 Referral letter

Note that owing to language issues, the health worker at the distant site may not speak or read the referring site's language, and may not be able to read the referral letter or treatment card of the referring site. Use generic names and terms such as stavudine, tuberculosis, cryptococcal meningitis and internationally agreed upon abbreviations or acronyms such as PMTCT or VCT (voluntary counselling and testing). Referral letters may get lost. Therefore, explain the contents of the letter to the patient, so they can relay information verbally if necessary.

4.3 OTHER IMPORTANT ISSUES

4.3.1 Cultural issues

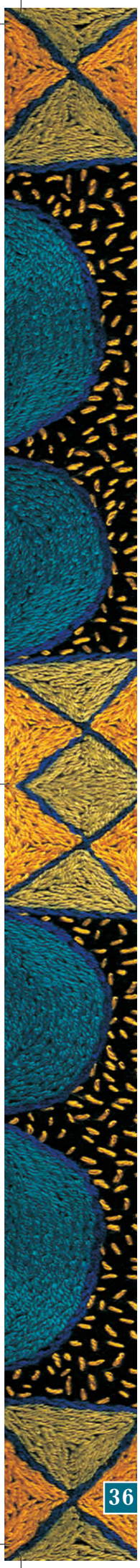
The background and culture of a displaced person may be different to that of the host country. Health workers should be culturally sensitive and non-judgemental. Regardless of cultural traditions or practices, the health worker should maintain professional standards and practices, although this may require additional time and effort. For example, if a man insists on knowing the HIV test results of his spouse without her consent, as this is his 'right' according to his culture, a more detailed explanation of the principles of confidentiality and disclosure may be required.

4.3.2 Alternative treatments

As with many local communities, displaced persons may seek alternative treatments. Encourage them to share this

'People come to us frustrated and disillusioned after being turned away from the hospitals repeatedly.'

South African NGO working with displaced persons



information with the health worker, so that informed treatment decisions can be made. In almost all cases, drug interactions between ART and alternative medication are unknown, and alternative medication should be discouraged where possible.

4.3.3 Psychosocial and mental health[8]

Displaced persons, particularly those coming from conflict areas, may have experienced trauma and violence, including sexual violence, and therefore may be in need of specific psychosocial support. These issues should be explored sensitively and efforts to refer to specialised services should be made.

History taking may provoke anxiety, depression and stress responses. Appropriate counselling should be made available.

4.3.4 Prevention

Southern Africa is an area of very high HIV prevalence. In some cases, displaced persons will be moving into a high HIV risk or higher prevalence environment (e.g. from Somalia to South Africa). Displaced persons should be made aware of increased HIV risk. Some populations have very limited knowledge of prevention methods, such as condoms, and health workers must not assume core knowledge exists.

For those already living with HIV, prevention messages must be re-emphasised to avoid further infections.

Prevention messages, verbal or written, must be communicated where possible in the displaced person's language.

The essential linkage between prevention and treatment is as relevant in this situation as with the host general population.

4.3.5 Reproductive health[9]

Family planning availability needs to be carefully explained. Issues such as access to contraception, termination of pregnancy, emergency contraception and availability of ante/postnatal care should be outlined for all displaced persons.

Specific care options may not be known to the person due to unavailability in area of origin (e.g. contraceptive methods, Pap smears); these new options should be explained.

4.3.6 Gender-based exploitation and violence[10]

Sexual violence often accompanies conflict and consequent displacement.

Displaced persons are often economically vulnerable, and may be at increased risk of sexual exploitation and abuse. In particular, women and girls may be more susceptible to HIV due to gender discrimination and violence, insufficient access to HIV prevention information and services, inability to negotiate safer sex and lack of female-controlled HIV prevention methods.

Information anticipating this, especially regarding PEP and psychosocial support, should be provided.

A careful and sensitive history should be taken in all cases. In cases of prior sexual assault, appropriate systematic care, support and treatment should be initiated, as per national guidelines.

4.3.7 Orphans, separated and vulnerable children

The nature of displacement often results in family separation. There may be an increase in orphans due to conflict and a related increase in communicable diseases. Displaced children may also be accompanied by a relative or another adult who is not a relative. If there are any concerns regarding the guardianship or care arrangements for the child, refer directly to social services for assessment.

Specialised counselling may be required for these children.

Red Cross/Red Crescent and other organisations facilitate tracing of family members and return of children to their country of origin.

Consent issues are covered in the paediatric treatment section (see section 4.1.5).

4.3.8 End-of-life care

Treatment options closer to the person's home may need to be explored in the event of limited mobility. Palliative care options vary, and support is often available in the host country through government programmes and NGOs.

Refugees wishing to return to their country of origin should contact UNHCR.

4.3.9 Death and body disposal

Body transport across borders may be expensive, logistically complex and bureaucratic. International organisations rarely facilitate the transport of a body to the home country, although faith-based organisations may.

In the case of terminal patients, this information should be sensitively explained to the patient and their family members, and any available support offered.

4.4 ADVOCACY

Health workers should advocate for non-discriminatory medical practices, and must play an active role in reducing discriminatory attitudes and dispelling myths regarding displaced persons.

Concerning refugees and asylum seekers, many countries in southern Africa, such as Namibia, South Africa and Zambia, have specific policies that include these groups in their public sector ART programmes. Others, such as Mozambique, Malawi and Zimbabwe, do not specifically exclude refugees or asylum seekers from public sector ART. As at March 2007, Botswana is the only country with a policy that specifically excludes non-nationals from the ART programme. However, UNHCR and other organisations are advocating the government to lift this restriction.

Where policy restrictions exist precluding ART access in the public sector, migrants, refugees and others should be referred to NGO, faith-based or private sector ART programmes.

5. CASE STUDIES

Case 1: Thembi

Thembi is a Botswana national who has a work permit for South Africa (SA) and is working there as a cashier. She has just arrived in South Africa, after spending a year on the Botswana national programme. She has lost her referral letter and only plans to return to Botswana in 6 months. She says she is on tenofovir, 3TC and nevirapine, dosed daily, and is considering having a child with her South African husband. She was previously on d4T, but developed a peripheral neuropathy and was switched to tenofovir. She has sufficient medication for an additional week.

She is refused access to the ART site in the government programme in SA, as it is not available to economic migrants. She goes to a private practitioner, but does not have money to pay for a viral load or CD4 count. The practitioner is unable to obtain the records from the Botswana site. Clinically she is well. She claims complete adherence and says that her previous viral load, taken 6 months ago, was 'OK'.

The practitioner advises her that tenofovir is not yet readily available in SA. d4T is not an option, due to her previous peripheral neuropathy, nor is ddI, both substitutes for tenofovir. AZT and abacavir are options as substitutes, although abacavir remains very expensive, and AZT ideally requires haematological monitoring, with attendant costs.

Introducing a single new drug to replace tenofovir in the face of a virologically failing regimen carries the risk of resistance to that drug, if no viral load is obtained to confirm suppression.

The practitioner persuades Thembi to pay for a single viral load, funded through her local church. The result comes back undetectable. He substitutes tenofovir with AZT, carefully explaining the new twice-daily dosing she now requires. She asks why other patients are on efavirenz, and why she isn't. The practitioner explains that established nevirapine is very safe, and that a switch is not advised, especially if she plans to have a baby, due to concerns regarding the teratogenicity of efavirenz. He asks her to try to obtain her past medical records as soon as possible. Thembi is advised to return if she experiences any side-effects, and is asked to see if the church has further resources to pay for haemoglobin and further viral load monitoring.

Case 2: Machozi

Machozi is a 28-year-old married woman from Eastern DRC. Like most of the women in her area, she has never been to school. Four years ago, she was working in her fields when a group of soldiers moved through the area. Seeing her in the field, they took her hostage and forced her to carry their goods. They then forced her to 'marry' one of the commanders.

Over the next 4 months she was repeatedly raped. Finally she was able to escape her captors, and in fear of being re-captured, she fled over the border of Zambia. She settled in a small town and made a meagre living selling items in the market. Then over several months, she started to lose weight. She noticed as well that her skin had broken out in a rash that wouldn't go away. At first she thought she had been poisoned by one of the market women but finally the nurse at the health centre convinced her to have an HIV test. The test was positive and she was referred to the HIV clinic.

The doctor who saw Machozi at the clinic evaluated her as clinically WHO stage 3. He prescribed co-trimoxazole and ordered a CD4 count. The CD4 came back as 124, and the doctor decided to start preparing Machozi to start ART. However when he discussed this with Machozi, she didn't seem to understand. In fact, she told the doctor that she had decided to return home, and therefore could not come back to the clinic. The doctor explained how important it was to stay in Zambia and start ART. Machozi nodded, but still insisted that she must go home. She told the doctor she would take the pills home with her if they were so important.

The doctor considered this option. Machozi was newly diagnosed and while she seemed to understand her diagnosis, the doctor could not be sure, given the language difference and the short time he had known her. A pill count of her co-trimoxazole showed that she had some pills left over. He asked Machozi to describe the health care in her home village. Machozi described the small basic health centre with a single nurse in the town one hour's walk away. She described how much it cost to see the nurse and how often there were no drugs in the health centre. Considering Machozi's current state of preparedness for ART, the uncertainty that lay ahead when returning home, and the poor level of the local health care system, the doctor decided not to start Machozi on ART before leaving. Instead, he advised her to try and seek out an NGO HIV programme when she returned home. He gave her a 3-month stock of cotrimoxazole tablets and reviewed again with her how to take the pills correctly. Finally he wrote a letter describing her medical history and explained its contents to her.

6. KEY DOCUMENTS

United Nations High Commissioner for Refugees. *Note on HIV/AIDS and the Protection of Refugees, IDPs and Other Persons of Concern.* Geneva: UNHCR, 2006.

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DISPLACED PERSONS AND HIV CARE: CHALLENGES AND SOLUTIONS

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Countries in southern Africa host a variety of displaced populations: refugees and asylum seekers who have fled conflict or persecution in their country; internally displaced persons who are still within their country; and economic migrants moving in search of employment. Regardless of the reason for displacement, all persons have the right to the '*highest attainable standard of health*',[1] including HIV-related care. However, the displaced person's ability to access care can be fraught with challenges. They often do not speak the language in the area to which they have moved. They might not be familiar with local systems or services. They may have knowledge gaps, particularly related to HIV and AIDS, and have specific support needs owing to lack of traditional community and family support structures. But one of the greatest barriers to access to care is one that can easily be surmounted: reluctance on the part of health professionals, from nurses to clinicians, to make the extra effort necessary to deliver services to such individuals.

The reasons for this reluctance are varied. Certain myths about displaced persons persist, such as the belief that they are more likely to engage in high-risk behaviour, or that they are too mobile to adhere to antiretroviral therapy (ART) and therefore pose a risk of developing resistance. None of the available evidence supports these perceptions; on the contrary, the evidence we have for refugee populations, for example, demonstrates fewer risky behaviours in comparison with the host community.[2,3] However, every situation is context-specific and must be evaluated as such.

By the end of 2003, refugee populations remained in their host country for an average of 17 years.[4] Furthermore, behavioural surveillance surveys show a high level of interaction between refugee and host communities; clearly the exclusion of displaced persons from local HIV and AIDS-related services is detrimental to efforts in HIV prevention, care and treatment to both displaced persons and the surrounding host communities.[5]

According to the World Health Organization (WHO), the largest threat for developing resistance to ART is persons taking their medications in an incorrect manner;[6] this threat is no larger for displaced populations than for other populations.

Differing treatment regimens and treatment interruption between area of origin and area of displacement may also pose a challenge to clinicians. However, clear guidance on this issue has been developed through a consultative process led by the Southern African HIV Clinicians Society and UNHCR (included in this issue of the journal).

Clinic in Zambia serving refugees and locals, 2006 (J Redden, UNHCR).

Lack of awareness of the rights of displaced persons, together with xenophobia, can lead health professionals to deny care. In a survey conducted among urban refugees in South Africa in 2003,[7] 30% of respondents who had been denied emergency medical care, which is guaranteed to everyone under the national Constitution, reported that the denial came directly from a doctor or a nurse. The reasons given varied, but many practitioners showed a lack of familiarity with refugee rights, as well as a belief that such services were 'only provided to South Africans'.

In fact, the HIV care needs of displaced persons are, for the most part, not different to those of local patients; a bit of empathy and creativity will go a long way towards finding ways of providing the same quality of services to these populations. In a number of countries in the southern African region, creative approaches to some of these challenges have already been employed. In Botswana and South Africa, local non-governmental organisations (NGOs) maintain a roster of trained interpreters to help with communication and adherence support. In Mozambique and Namibia, UNHCR and its NGO partners provide support for transport from refugee camps to the nearest ART site. UNHCR has also produced or translated existing HIV information materials into local refugee and migrant languages. These materials are a very effective means of educating patients, whether dealing with prevention, care or treatment. The only problem was language, which again, with a bit of initiative, has been quite easily overcome.

Displaced boy, Luena, Angola, 2006 (J Redden, UNHCR).

WHO, together with UNHCR, UNICEF and other international organisations, recently held an expert consultation on delivering antiretrovirals in emergencies. In the consensus statement from this meeting, they conclude:

'That emergencies ... should not affect one's access to HIV services and that the provision of such services is not only feasible, but an inalienable human right and a public health necessity.'[8]

HIV knows no borders, nor individuals. Addressing the HIV-related needs of displaced persons in an equitable, non-discriminatory manner is a critical intervention in the fight against HIV and AIDS, particularly in sub-Saharan Africa.

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ETHICS CASE STUDY

DISCLOSURE OF DOCTORS WITH HIV/AIDS ON ANTIRETROVIRAL THERAPY

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The Southern African HIV Clinicians Society initiated an online discussion forum on 'HIV Ethics and Policy' in 2007. The first case study concerned the ethical question of whether a surgeon with HIV/AIDS on antiretroviral therapy should have disclosed her HIV status to her patient when she discovered blood on the inside of the first of her double gloves after surgery. The case study, and some responses submitted to the forum, follow below.

CASE STUDY 1

AA is a medical doctor and practises in South Africa. While still in training some years ago, she had a needle-stick injury followed some weeks later by a seroconversion illness. At the time antiretrovirals (ARVs) were unavailable, and indeed the diagnosis was missed: it was the late 1980s and she was working in a mine hospital. Some years later AA discovered her HIV status while trying to obtain insurance cover. She was referred to Dr T a few years later when her CD4 cell count had fallen. Since the mid-1990s AA has been on ARVs – almost all available ARVs have been used over this 10-year period. In 2006, her CD4 count was above 500/µl and her viral load has been undetectable for many years.

In the middle of 2002, AA called Dr T to report that after doing a surgical procedure earlier in the day, she had noticed some blood on the internal glove during de-gloving. She had double-gloved and the blood was seen after the first glove was removed. When she took off the next glove, however, she could not find any laceration on her own finger (below the site of the blood on the glove), and she therefore assumed that the blood was the patient's and not her own. (The procedure had involved the insertion of a needle into a large vein in the neck of the patient, and had been uneventful apart from quite a bit of bleeding from the operative site. A nurse had had to compress the area for several minutes at the end of the procedure to arrest the haemorrhage.)

AA asked Dr T's advice on the following

- whether he thought she should inform the patient of the incident;
- was there any likelihood that the blood in the glove was actually hers, and
- might there be a possibility that the patient had been exposed to her blood and possibly to the HIV virus?

At the time, AA viral load was undetectable and she was on round-the-clock ARVs.

Dr T expressed the opinion that that it seemed unlikely that the patient had been exposed to the doctor's blood and that post-exposure prophylaxis (PEP) was not indicated for the patient. Disclosure to the patient would mean the possibility that the doctor's HIV status would become known beyond her immediate family and Dr T, and that her medical practice and livelihood might be jeopardised. It seemed that the risk to the patient was not significant or measurable. Dr T counselled against informing the patient of any risk and against initiating PEP.

Three months later Dr T was asked to see a patient who had recently been diagnosed as HIV positive. He was the man on whom the surgical procedure had been carried out by AA. Blood tests revealed recent exposure to the virus: initially negative HIV antibody tests (HIV Elisa) but with an extremely high viral load. The HIV Elisa subsequently became positive. The patient started on ARV therapy and has remained well. He noted that he had had a range of sexual partners, and believed that one of these might have infected him.

Some time later the patient returned to Dr T. He was perplexed. He had seen all of his sex partners, and each had tested HIV-negative. 'Doctor, where did I get this infection?' he asked Dr T. 'Do you think that it might have been at the time of the medical procedure some months earlier?' He recalled that there had been a lot of bleeding from his neck following the operation, and that a nurse had 'stuck her finger in the hole to stop the bleeding'. He asked whether he could have got the infection from the nurse.

Dr T has been unable to DNA-fingerprint AA's virus owing to its being undetectable. Dr T wanted to confirm resistance mutations that might identify whether the patient's and AA's virus are the same. The patient's viral genotype revealed a fully sensitive HIV-1 virus, and he has achieved viral suppression on first-line ARV therapy. AA had viral genotyping several years ago when she showed evidence of resistance. Her virus has multiple resistant mutants, and for some years now she has been maintained on 'salvage

therapy' with drugs that are currently unavailable commercially in this country.

1. What is the likelihood that the patient was infected by AA?
2. With the facts available to him, should Dr T have suggested that AA's patient go onto PEP?
3. Should AA disclose her status to the patient?
4. Should the role of the nurse and sexual partners help provide answers to the questions posed above?

CASE STUDY RESPONSES

A – SUBMITTED BY JOHN GOSLING

Given that AA's viral load is undetectable and her genotype appears to be different from the patient's (although her genotype had not been determined recently), and given the circumstances described related to the procedure, it seems unlikely that she is the source of the infection. For a variety of reasons it does not seem to me appropriate for her to reveal her status to the patient. Given the available facts, I would also support Dr T's decision not to recommend that the patient go onto PEP following the procedure.

The possible role of the patient's sexual contacts remains potentially problematic. It would appear that he does not practise protected sex. He claims to have checked with all his recent sexual contacts, but there is no guarantee that they are all being truthful about their status, and it is not clear if he found out when they had last had an HIV test. Furthermore, there is the question of the 'window period' following infection.

The following points related to the window period are informative. Antibody tests that are currently being used are more sensitive than those used in the past. Most people will develop detectable antibodies by 30 days after infection with HIV.[1,2] Nearly everyone who is infected with HIV (99%) will have detectable antibodies by 3 months after infection.[2] It is rare for people to take longer than 3 months, but the possibility does exist.[3]

It is not clear when exactly the patient determined that he was HIV positive and how this diagnosis was made, as he was initially negative for HIV antibodies when tested by Dr T. Is it possible that his infection and subsequent seroconversion was more recent than the surgical procedure, given that most people will develop antibodies within 30 days? It seems to me that this is highly likely. One of his recent sexual contacts might have been in the highly infective window period, and had not yet tested positive. This seems a very real possibility to me.

The nurse who 'stuck her finger into the wound' to stop the bleeding may also be a potential source of the infection, though this seems unlikely. Was she wearing gloves (I assume she was), and do we know her HIV status? (It would be unethical to insist that she disclose her status – she would need to reveal it voluntarily.)

B – SUBMITTED BY SUSAN BLACK

The doctor who was infected with HIV should not have been practising medicine that required scalpels, cutting or neck insertions, which can be very bloody. In this situation it would be difficult to see a small prick on one's finger.

Despite this:

- *What is the likelihood that the patient was infected by AA?*
  It is very unlikely that the patient got HIV from the doctor.
- *With the facts available to him, should Dr T have suggested that AA's patient go onto PEP?*
  Dr T should have advised PEP for the patient. Honesty is the best policy, and at least the doctors would have felt that every precaution had been taken in this case.
- *Should AA disclose her status to the patient?*
  AA should disclose her status to all her patients, and it is their decision whether or not they continue their care with her.
- *Should the role of the nurse and sexual partners play a part in providing answers to the questions posed above?*
  The role of the sexual partners and the nurse has no consideration in this case. Our concern is with the ethics of the doctors, and they were self-serving.

CONCLUSION – DAVID SPENCER

This is a difficult case. The replies from colleagues reflect the difficulty all of us have in deciding between altruism and self-interest. Neither AA nor her doctor were able to cross this line and simply tell the patient of the incident and offer PEP. There is a line here: doctors are also entitled to their privacy, and persons who are HIV positive are entitled to the maintenance of confidentiality. (And where there is a realistic chance of exposure and transmission, our patients need to be protected.) Confidentiality and privacy and individual rights apply as much to health professionals who are infected as to the general public. By informing the patient of his possible exposure to her blood, the doctor in this case would almost certainly have forfeited her right to privacy and possibly to the practice of her profession. Did the circumstances of this case justify the doctor placing herself and her family and her future ability to earn an income at such a risk?

The medical facts support the view that the virus was not transmitted through this exposure: the doctor's viral load was undetectable, the patient's virus demonstrated sensitivity to ARV agents to which the 'possible' source is resistant, and to the best of my knowledge there is no similar case resulting in transmission reported in the current scientific literature. It is generally accepted that exposure to blood in a hollow-bore needle carries a 0.3% risk of transmission and exposure to a blood splash on a mucous membrane or open lesion a risk of 0.09%, i.e. 9 in 10 000 exposures. The exposure described here

is ill-defined: whose blood was on the inner glove? The doctor had no visible laceration or source of bleeding. Blood at the site of the procedure is likely to have been the patient's: this is usually the case. The insertion of a central intravenous line, while at times bloody, seldom demands any protracted contact between patient and doctor. And during such procedures the doctor's finger is visible at all times: this was not deeply invasive surgery requiring the hands of the surgeon to be buried deep inside the patient's body. The likelihood of there having been sufficient opportunity for transmission of virus must be very small, probably less than that of a mucosal splash. How does one measure that level of risk? Is there really a risk?

In counselling for post-exposure prophylaxis it is important to be able to measure risk. The level of risk under the circumstances as described in this case does not appear to warrant PEP.

The patient is sexually active with multiple partners. That he asked them for proof of their HIV status suggests that risks had been taken in these relationships. Although these partners all tested negative, we are not informed whether the patient had other partners during the period of likely exposure or whether there has been any follow-up of his partners subsequent to the initial tests. It would be important to clarify these matters, and one could still do this.

Should the doctor disclose her HIV status to her patients (and obviously then to the staff with whom she works, and to others with less personal interest in her well-being?) Clearly this is not necessary. (It may become necessary where the risk of exposure is definite and where PEP is clearly indicated.) Nevertheless the point is taken that the infected health professional must be encouraged to work in medical disciplines that require very little participation in invasive procedures.

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POLICY AND ETHICS REGARDING HIV

DISCUSSION FORUM

'In an era of failed development projects, and economic policies gone bad, I sometimes feel very lucky as a physician, since my experience in Haiti has shown me that direct services are not simply a refuge of the weak and visionless, but rather a response to demands for equity and dignity.' – Paul Farmer

Have you ever wondered:

- Whether the AIDS epidemic in Southern Africa requires a different set of ethics?
- About the patient's dilemma when she has to choose between ARVs and losing her disability grant?
- Whether mandatory HIV testing is the new panacea, or a ridiculous polemic?
- About dual loyalties when faced with manifestations of government AIDS denialism?
- About the regulation of traditional health practitioners and the implications for AIDS care?

Then join the policy and ethics online discussion group. To view the discussions so far, go to http://groups.google.com/group/policy-ethics

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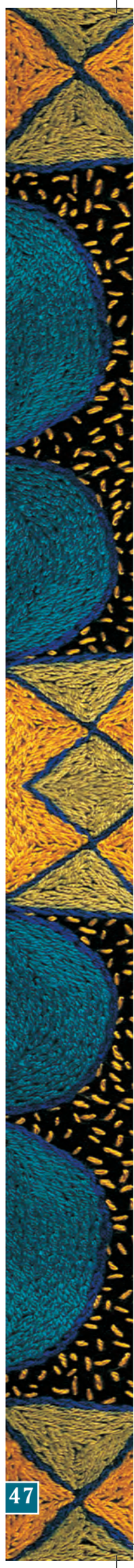

PAEDIATRIC CASE STUDY

AN HIV-INFECTED INFANT WITH BACILLE CALMETTE-GUÉRIN DISEASE, RECURRENT AND MULTIDRUG-RESISTANT TUBERCULOSIS COMPLICATED BY ACUTE COR PULMONALE AND HEPATITIS WHILE ON ANTIRETROVIRAL THERAPY

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We describe the management of an HIV-infected infant with multisystem disease. The infant presented with severe disease at 3 months of age. Initiation of antiretroviral therapy (ART) was delayed through initial lack of access, after which she developed immune reconstitution inflammatory syndrome to BCG. At this time she was also infected with *Mycobacterium tuberculosis*, with a later recurrence due to multidrug-resistant (MDR) tuberculosis (TB). During this episode she presented with acute cor pulmonale, possibly due to a pulmonary embolus and also transaminitis. Although such infants are seen frequently in sub-Saharan Africa, there are few guidelines or case descriptions to assist clinicians.

There are reports of clinical experience with complex diagnostic and therapeutic issues in HIV-infected children from sub-Saharan Africa where TB is endemic, drug-resistant TB is increasing and disseminated Bacille Calmette-Guérin (BCG) disease after immunisation is a recently recognised complication. We describe an infant with chronic lung disease, BCG adenitis due to the immune reconstitution inflammatory syndrome (IRIS), recurrent TB and suspected pulmonary embolism complicated by *Escherichia coli* sepsis, intracardiac thrombus and hepatotoxicity while receiving highly active antiretroviral therapy (HAART) and antituberculosis therapy. The second episode of TB was due to reinfection with an MDR *M. tuberculosis* strain. The purpose of this report is to broaden the experience of clinicians managing infants under similar circumstances.

CASE PRESENTATION

The infant presented at 3 months of age with *Pneumocystis jiroveci* pneumonia (PJP), multiple skin abscesses, oral candidiasis, chronic gastroenteritis and failure to thrive. An enzyme-linked immunosorbent assay for HIV antibodies and a polymerase chain reaction for HIV-1 RNA were positive. Both parents were also HIV-seropositive. Her HIV disease was classified as Centers for Disease Control (CDC) stage C-3.[1] The absolute CD4+ T-lymphocyte count was 101×10^9/l (10%). Owing to financial constraints, plasma HIV RNA was not quantified. HAART, consisting of ritonavir (RTV), didanosine (ddI) and stavudine (d4T), was commenced at $4\frac{1}{2}$ months of age. Therapy was funded through a charitable donation as at the time (2002) HAART was unavailable for children in public hospitals. Three weeks after initiation, she developed BCG IRIS presenting as right axillary lymphadenitis. *M. tuberculosis* complex was cultured and *M. bovis* BCG identified by PCR.[2,3] The lymph node developed into a massive local abscess, which was eventually drained.[4] At the same time *M. tuberculosis*, susceptible to isoniazid and rifampicin, was cultured from gastric aspirates taken at 4 months of age because of a cavity noted on chest radiography. The Mantoux tuberculin skin test showed no reaction at 4 and 6 months of age. Her mother was subsequently discovered to have active TB. Antituberculosis treatment with rifampicin, isoniazid, pyrazinamide,

ethambutol and ethionamide was commenced. Three follow-up cultures for *M. tuberculosis* were negative following 6 months of treatment. Treatment with all 5 drugs was continued for 8 months and then stopped following a good clinical response, with increased weight for age standard deviation score increasing from –3 at 6 months to –1 at 15 months.

Two months later, at 16 months of age, the patient presented with acute pneumonia (cough and difficult breathing for 2 days). A chest radiograph showed new alveolar opacification and a large cavity in the apex of the right lower lobe. In addition to antibiotics, a second course of antituberculosis treatment was started with the same drugs as before, as both she and her mother had documented drug-susceptible TB.

At 19 months of age she presented with acute onset of severe dyspnoea. Medication at this stage consisted of co-trimoxazole prophylaxis, antituberculosis treatment and HAART. Adherence to all medications including HAART was excellent, with calculated adherence for HAART in the previous 6 months between 93% and 152% (mean 118%).

Physical examination showed an afebrile well-nourished, acutely ill child. Her systemic blood pressure was 100/62 mmHg. There was severe tachypnoea and dyspnoea and signs of long-standing lung disease (clubbing and Harrison's sulci). The transcutaneous O_2 saturation was 90% with 6 l O_2/min administered by face-mask. Her chest was hyperinflated without adventitious sounds. Cardiovascular examination revealed a normal S1 and a loud S2. Peripheral circulation was adequate. There was mild hepatomegaly and splenomegaly. The neurological examination was normal.

M. tuberculosis was again confirmed on the gastric aspirate culture done at 16 months. As her weight gain had been good, current treatment was continued while awaiting mycobacterial drug susceptibility test (DST) results. The chest radiograph showed increased heart size compared with previous chest radiographs, new-onset hyperinflation and a bilateral diffuse nodular appearance in the lung fields, noted 3 months earlier, but no cavities. Laboratory investigations revealed a white blood cell count of 13.4×10^9/l (7.1×10^9 neutrophils and 4.8×10^9 lymphocytes), haemoglobin 11.1 g/dl, platelets 203×10^9/l and C-reactive protein (CRP) 65 mg/l. There was a marked increase in levels of aspartate-aminotransferase (7 280 IU/l) and alanine-aminotransferase (2 283 IU/l). The urea level was 4.4 mmol/l (normal range 1.1 - 5 mmo/l) and the creatinine level 54 µmol/l (normal range 35 - 62 µmol/l). The blood gas showed a pH of 7.3, pCO_2 of 6.28 kPa and base excess of –2.8 mmol/l. The anion gap was 18 mmol/l. Blood lactate was not measured. The bilirubin (total –57 mmol/l, unconjugated fraction 28 mmol/l) was mildly elevated. The CD4+ T-lymphocyte percentage was 26% (absolute number 1.2 x 10^9/l) with a CD4/CD8 ratio of 0.68:1. Urine was not cultured. Serology for hepatitis A, B and C was negative.

The differential diagnosis included pneumonia (bacterial, viral, tuberculosis or PJP) and pulmonary hypertensive crisis. The hepatitis was ascribed to hepatotoxicity secondary to HAART and antituberculosis medication, aggravated by sepsis and congestive cardiac failure.

Cefuroxime (100 mg/kg/d intravenously) was prescribed for bacterial pneumonia. Co-trimoxazole dosage was increased to 20 mg/kg/day of the trimethoprim component for possible PJP and hydrochlorothiazide (2 mg/kg/d) was commenced for pulmonary hypertension. HAART was discontinued due to hepatitis and antituberculosis therapy was changed to amikacin, ofloxacin and ethambutol.

E. coli was cultured from blood. An electrocardiogram showed sinus rhythm and right-sided ventricular enlargement. Echocardiography showed right atrial and ventricular enlargement. The pulmonary arterial systolic pressure was 76 mmHg, indicative of severe pulmonary hypertension. A round echogenic mass, diameter 6 mm, was visualised in the right atrium just below the superior vena cava, compatible with a thrombus. Identification of *E. coli* from blood implied that the mass might be infected. Amphotericin B and anticoagulation therapy (heparin and warfarin) were commenced. The liver enzymes normalised rapidly after discontinuation of the HAART and altered antituberculosis therapy, and the respiratory distress improved gradually.

Fundoscopy showed no signs of systemic fungal infection, and repeated blood cultures remained negative for fungi. A ventilation-perfusion scan of the lung performed 9 days after admission showed low intermediate probability (30%) of a pulmonary embolus in the anterior basal segment of the left lower lobe. Repeat echocardiography a day later still showed pulmonary hypertension, but the right atrial mass had disappeared. Eight weeks later the pulmonary hypertension had also resolved. Oxygen therapy was discontinued.

After the hepatitis resolved, the original antituberculosis drugs were gradually re-introduced. This was changed to MDR TB treatment with ethambutol, ethionamide, ofloxacin, amikacin and terizidone after the drug susceptibility test pattern confirmed resistance to isoniazid and rifampicin after 3 months. Thereafter, HAART was restarted uneventfully. Coagulation studies 12 weeks after admission were normal except for a marginally low protein C. MDR TB treatment was continued for 15 months. The patient was clinically cured, confirmed by several negative cultures and calcification on chest radiograph.

Strain identification by standardised DNA-spoligotyping[5] confirmed re-infection with a different strain of *M. tuberculosis* to the initial isolate.

DISCUSSION

This case illustrates the difficulty of diagnosing and managing TB in HIV-infected children, even in a region where TB is endemic and physicians have a high index of suspicion for TB. The case also emphasises the importance of regular DSTs for *M. tuberculosis* isolates. The diagnosis of TB was first made in the infant a month after the gastric aspirate was taken.

Because BCG adenitis was clinically suspected and *M. bovis* BCG is intrinsically resistant to pyrazinamide, ethambutol and ethionamide were added to the treatment regimen. These decisions were vindicated by detection of both *M. bovis* BCG and *M. tuberculosis* infection.

The patient presented with a second episode of pulmonary TB due to reinfection with an MDR *M. tuberculosis* strain. At this time there was no reason to suspect MDR TB, as the previous isolates were susceptible. Inappropriate treatment of MDR TB initially may have contributed to the complicated course during the most recent admission. Confirmation of susceptibility may take 2 - 3 months, during which treatment decisions are required. Recurrence of TB is not uncommon in HIV-infected children in this highly TB endemic area, where the annual notification rate was 638 cases/100 000 population in 2003.[6] Both reinfection and relapse occur.[7] In this patient, reinfection with an MDR *M. tuberculosis* strain was confirmed by DNA fingerprinting.

The management of MDR TB cases is difficult and mortality is usually high, especially in HIV-infected patients. Although the DST pattern only showed resistance to isoniazid and rifampicin and was susceptible to ethambutol, the treatment regimen included all available second-line antituberculosis drugs, as she had previously received 5-drug treatment and now presented with cavitating disease, indicating higher organism load and the danger of development of further drug resistance if not managed appropriately. Treatment was continued with all drugs except amikacin for 12 months after the first negative culture.

BCG IRIS-related suppurative adenitis occurs fairly commonly after initiation of HAART.[8] The BCG abscess responded well to the combination of surgical drainage by aspiration of the abscess, antituberculosis treatment and continuation of HAART. Dual infection with *M. tuberculosis* and BCG has also been described[4] and this case illustrates the importance of retaining pyrazinamide until *M. tuberculosis* has been excluded.

While on HAART and treatment for the second TB episode, the infant developed hepatotoxicity. Both regimens contain hepatotoxic drugs and physicians should be alert to this complication. As drug hepatotoxicity could be fatal, all potentially hepatotoxic drugs were discontinued and reintroduced sequentially after hepatic enzymes had normalised. At the same time, *E. coli* sepsis and acute cor pulmonale possibly due to a pulmonary embolus was diagnosed. The disappearance of the mass could have been due to dislodgement or fibrinolytic activity (either intrinsic or exogeneous). Its disappearance in 10 days excluded a malignancy, and the multiple negative fungal blood cultures make a fungal aetiology unlikely. We could not definitively diagnose pulmonary embolism as the VQ scan showed only a 30% probability. A pulmonary embolus is compatible with the clinical course, showing gradual improvement of respiratory distress and eventual normalisation of pulmonary pressures. Hypercoagulability has been described in patients with HIV and also tuberculosis.[9,10]

CONCLUSION

This case reflects the difficulties in management of children with advanced HIV disease. The patient had an especially complicated course preceding and after the introduction of HAART. TB and its complications require vigilance in HIV-infected children and clinical decisions may precede laboratory confirmations.

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OPINION

THE FIGHT AGAINST KAPOSI'S SARCOMA IN AIDS – LESSONS FROM BRAZIL

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This article presents a brief review on 'epidemic' Kaposi's sarcoma (KS), an AIDS-defining illness, and laboratory data obtained by a group of researchers from São Paulo, Brazil, concerning the aetiological agent of KS (human herpesvirus 8, HHV-8). Brazil earned international acclaim in the fight against AIDS, providing universal free access to antiretroviral treatment for all patients and promoting education programmes for blocking virus transmission/acquisition. Drawing on her experience, the author suggests the use of highly active antiretroviral therapy (HAART) to combat AIDS and KS in countries where both diseases are epidemic. The lessons learned by Brazil, a developing country, and the techniques used there might help sub-Saharan countries to fight HIV and KS/AIDS, decreasing morbidity and mortality in these geographical regions.

Since the begining of HIV pandemic 25 years ago, Kaposi's sarcoma (KS) has been detected in AIDS patients, and it is considered an AIDS-defining illness.[1,2] The first report on disseminated KS in younger homosexual men from the USA contrasted with the three forms of KS previously described in elderly persons from Mediterranean countries, in children and adults from the sub-Saharan countries, and in post-transplant patients receiving corticosteroid and immunossupressive therapies.[3] KS in AIDS patients assumed a more aggressive pattern, disseminating into the viscera and being associated with a greater likehood of death.

KS in AIDS or 'epidemic' KS has been detected worldwide and is related to mode of HIV transmission: high frequencies of KS have been observed among homosexual men and low frequencies among haemophiliacs, suggesting that a sexually transmitted agent could account for the tumour.[4-6] In fact, in 1994 a novel human herpesvirus provisionally called Kaposi's sarcoma-associated herpesvirus (KSHV) and more recently named human herpesvirus 8 (HHV-8) was detected in KS lesions from AIDS patients.[7] The same herpesvirus was subsequently detected in all forms of KS, classic, endemic, and iatrogenic.[3]

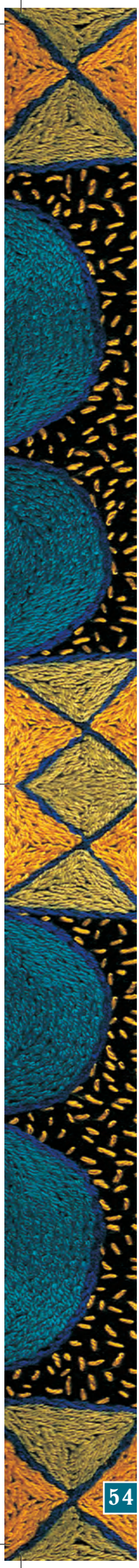
Interestingly, after the introduction of HAART, a reduction in the number of KS/AIDS cases was observed in the Western world.[8] *In vitro* and *in vivo* studies supported the benefit of antiretroviral therapy in controlling HHV-8 growth and disease development and progression.[9-12] The tat protein of HIV was implicated in enhancing the entry of HHV-8 into endothelial cells, and/or in increasing HHV-8 viral load by reactivation of HHV-8 from a latent state.[12,13] Antiretroviral therapy could therefore have a synergistic effect on KS/AIDS, allowing immune reconstitution and the clearance of HIV and consequently of HHV-8.

In 1994, antiretroviral treatment in AIDS patients was started in Brazil, first with transcriptase inhibitors, and from 1996 also with protease inhibitors. Since then, a decrease in the number of KS/AIDS cases has been detected by the Brazilian Ministry of Health. In São Paulo, Brazil, a seroepidemiological study conducted by our group in HIV/AIDS patients receiving antiretroviral therapy revealed 17% HHV-8-seropositive cases, and a 5-year follow-up showed that only 2% of these patients developed KS.[14] This result contrasts with the 20% prevalence of KS in AIDS patients detected in the same region before the HAART era. Taking these data into account, we advocated the use of antiretroviral therapy in developing countries where KS is endemic, such as in sub-Saharan Africa, in order to fight both HIV and HHV-8 infections and diseases.[15]

Since then we have been trying to detect HHV-8 infection in several populations from Brazil, searching for at-risk individuals, the HHV-8 subtypes, and the routes of virus transmission/acquisition. By means of in-house serological assays we were able to detect HHV-8-endemic populations among Amerindians from Amazonia,[16] homosexual/ bisexual men and promiscuous women,[14,17-19] and HIV-infected children.[20]

Using DNA sequencing of HHV-8 ORF K1 we were able to detect the three most common HHV-8 subtypes described around the world (A, B and C) in HIV/AIDS patients from São Paulo, south-east Brazil, and subtype B in a similar population from Salvador (north-east Brazil).[21-23] These data may reflect the ethnic background of the individuals who live in these regions; São Paulo received European and Asiatic immigrants during its colonisation and has a mixed race/colour population, while Salvador was colonised by black individuals from Africa during the African slave trade, so black/mullatto is the predominant population.

Furthermore, among Indians from the Amazon region (northern Brazil) we detected HHV-8 subtype E, which is phylogenically related to subtype D (Australasia) and subtype Hok (North of Japan), along with HHV-8 subtype A.[23] We



speculated that there could have been prehistoric migration of HHV-8-infected native populations from Asia through North America, reaching the North region of Brazil, resulting in the maintenance of HHV-8 subtype E in isolated populations from Brazil, but this hypothesis needs to be confirmed by phylogenetic analysis of several isolates.

Of interest was our finding of an alternative method for HHV-8 subtyping that utilises a restriction fragment length polymorphism analysis of ORF K1 (VR1) instead of sequencing assay.[21,22] This technique is able to rapidly subtype HHV-8, and it could be used in developing countries because of its low cost.

We still do not know whether there is a correlation between HHV-8 subtype and virus pathogenicity, but we are attempting to correlate HHV-8 subtype and tumour aggressiveness.

On the other hand, it seems evident that the routes of virus transmission differ between endemic and epidemic HHV-8 regions; sexual virus transmission could account for KS infection in adults from endemic and epidemic areas, and horizontal transmission for infection in children and infants from endemic areas.[3]

Using nested PCR for detecting several DNA segments of HHV-8, we confirmed HHV-8 shedding in blood, saliva, and urine from HIV/AIDS patients with and without KS, and suggested virus transmission/acquisition by these body fluids.[24] In addition, we recently found HHV-8 shedding in urine and suggested virus transmission in populations living in poor socioeconomic and sanitary conditions,[25] as previously demonstrated in a study conducted among Ugandan families with limited access to water and consequently poor hygiene.[26] Several sanitary practices that prevent contact with saliva and urine could therefore be employed in developing countries to avoid virus transmission/acquisition.

Brazil and Africa share several sociodemographic characteristics and sanitary conditions: South America and Africa are both large continents, their populations are educationally and socioeconomically diverse, rural and urban areas in both have very different populations and sanitary conditions, and both experience a large number of tropical and infectious diseases. In spite of this, Brazil has earned international acclaim in the fight against AIDS by a series of programmes including prevention and free access to antiretroviral treatment for all patients.[27,28] The lessons learned in Brazil, our experiences and the data we have gathered could therefore help developing countries to fight and control HIV/AIDS, especially in Africa where KS is endemic.

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CPD QUESTIONS

Journal 26

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

Please complete and post/fax to: Southern African HIV Clinicians Society, Suite 233, PostNet Killarney, Private Bag X2600, Houghton, Johannesburg, 2041, or fax (011) 453-5059

NAME ..... QUALIFICATION .....
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1. **With regard to XDR-TB, which of the following statements is TRUE:**
   (a) The extent of the XDR-TB problem in South Africa is well characterised.
   (b) XDR-TB appears to occur predominantly in patients previously treated for tuberculosis.
   (c) XDR-TB is a result of a failing national TB control programme.
   (d) XDR-TB is not contagious and infection control measures are not necessary to control spread.
   (e) XDR-TB can be diagnosed clinically.

2. **Which of the following statements is TRUE? According to a 2006 SADC/UNAIDS HIV Prevention 'Think Tank' Report, the main 'drivers' of the HIV epidemic in southern Africa are:**
   (a) low uptake of HIV testing
   (b) poor access to antiretroviral drugs
   (c) condom shortages
   (d) the common pattern of long-term concurrent partnerships (in which consistent condom use is uncommon) and lack of male circumcision.

3. **With regard to Hodgkin's disease, please indicate whether the following statements are TRUE or FALSE:**
   (a) Hodgkin's disease is the most common AIDS-defining tumour.
   (b) A high frequency of 80 - 100% of the Epstein-Barr virus has been identified in HIV-Hodgkin's disease patients.
   (c) The bcl-6 syn-1 positive Reed-Sternberg phenotype reflects the post-germinal centre B-cell origin in the HIV-infected population.

4. **Please indicate whether the following statements are TRUE or FALSE:**
   (a) South Africa is a signatory of the UN Convention on Rights of the Child, which obliges the government to act primarily in the best interests of the child when faced with competing maternal and child interests.
   (b) Antiretroviral drugs have been shown to reduce HIV transmission during breastfeeding.
   (c) Antiretroviral drugs can reduce risk of HIV transmission when given to newborns born to HIV-infected women who did not receive antiretroviral drugs.
   (d) PMTCT regimens in the Brazil public sector consist of a long course of 3 antiretroviral drugs, discontinued after childbirth in women not requiring ART for their own health.

5. **Answer 'TRUE' or 'FALSE':**
   Men from sub-Saharan Africa have a higher risk of HIV acquisition owing to a practice of multiple concurrent sexual partners.