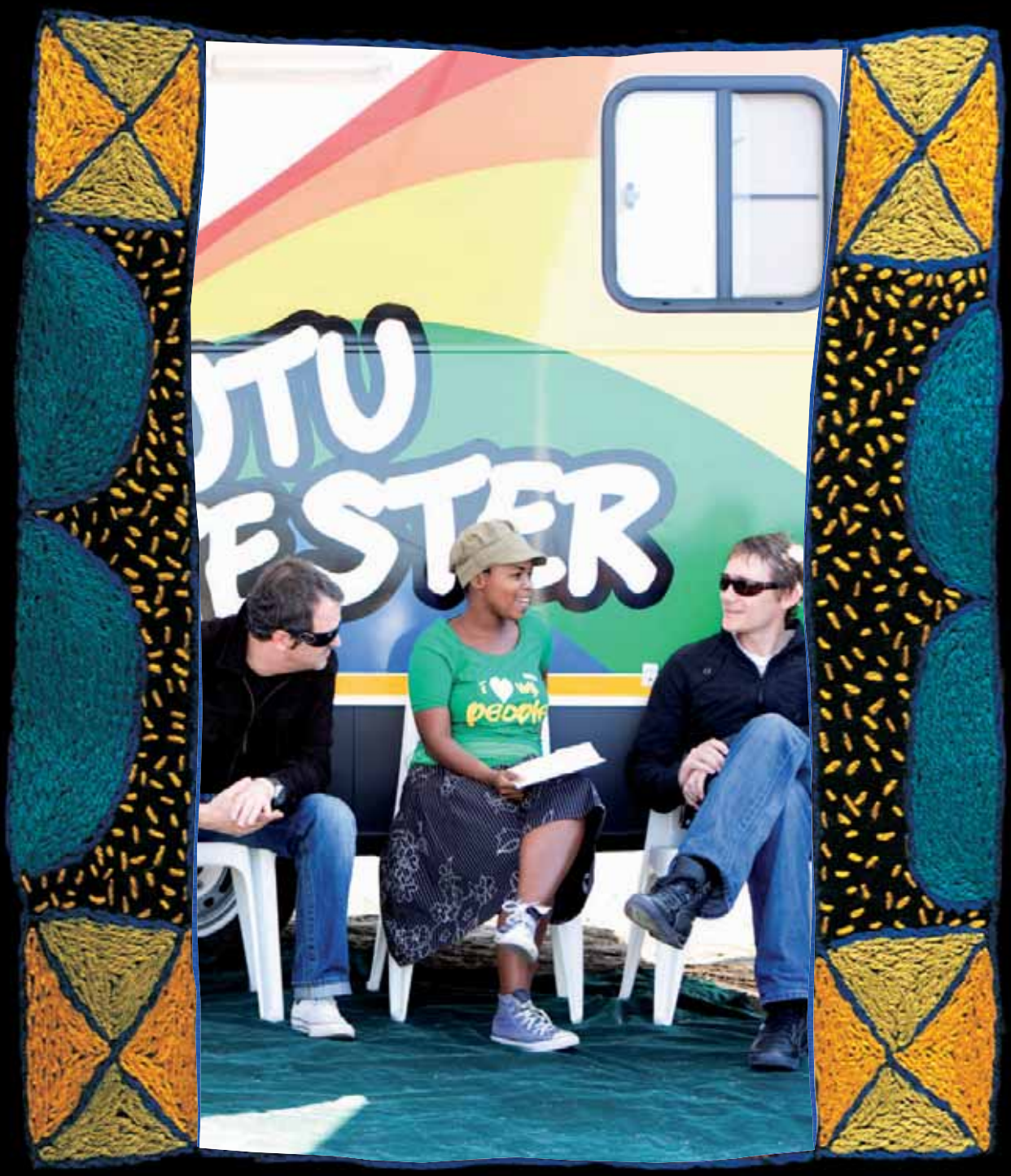
SOUTHERN AFRICAN JOURNAL OF HIV MEDICINE



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Cover: *Testing is key to the National Strategic Plan. The front cover photograph shows Zolani, Peter and Simon from the acclaimed South African band Freshlyground waiting to have their HIV tests done. The band participated in the Sunday Times 'Test One Reach Five Testing Campaign' and received their blood pressure, blood sugar and HIV test results from the Tutu Tester Crew when the mobile was in Masiphumelele, Cape Town, recently. The photographer is Jonx Pillemer, from Cape Town.*

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THE SOUTH AFRICAN MEDICAL ASSOCIATION

FROM THE EDITOR

It has been an incredible three months. As a Zimbabwean who came to this country and nailed my colours to the South African mast many years ago, I am as confused as many South Africans and most Africans at the events that have recently unfolded in this country. Why is it that human beings are so often intolerant? The HIV infected have also been been subjected to discrimination in the form of the 'New Apartheid', as Archbishop Tutu has called their alienation. I feel that some inroads are being made in this arena; that there is a better level of acceptance of those infected, facilitating much more openness to testing. Perhaps this provides a level of hope – that when we stop to understand what the issues are, get to the bottom of our fears and recognise that we all have much more in common than not, the prejudice begins to disappear.

This autumn edition brings an interesting smorgasbord of HIV information. We start off with a debate around paediatric testing and treatment and maternal rights. The case is presented by Cherisch and Richter and a rebuttal is given by Scorgie and colleagues. There is an opinion piece by Geffen and Gonzales (two well-known HIV activists) on rational activism. An interesting concept, and it is pleasing to see how activists can contribute so meaningfully to the scientific and policy debates in HIV. We also publish two sets of guidelines: importantly, one concerning treatment of prisoners, another marginalised and vulnerable group, and clinical guidelines for management of patients with renal problems in HIV. Wood and colleagues describe how the combination of a pharmacy data system together with field-based supporters can be used to improve retention in ART programmes, retention in programme being the next great challenge for our roll-out. Finally, colleagues from the Cochrane Centre, MRC , describe how medical research can be mapped in order to formulate medical policy. We also advertise the Southern African HIV Conference, to be held in Durban in early 2009. We hope to have a record number of abstracts and will provide a relevant and exciting programme.

Finally, our thoughts are with our Zimbabwean colleagues at this time.

LINDA-GAIL BEKKER

Editor

MESSAGE FROM THE EXECUTIVE

It has been a tough few months for government doctors. The disgraceful public attacks on doctors Colin Pfaff and Mark Blaylock by various KwaZulu-Natal politicians and bureaucrats have been met with unprecedented public and media anger (see http://www.sahivsoc.org/). Happily this has resulted, at least at the time of writing, in wiser political heads stepping in to stop unrestrained public statements by leaders responsible for the health care of almost a quarter of all South Africans.

It is a pity that the politicians did not pause to think, as the rural doctors in KZN have piloted several innovative programmes that creatively address both HIV and tuberculosis. The politicians were in a position to draw attention to the impressive successes of the Manguzi down-referral and primary care HIV programmes. KZN has shown impressive growth in antiretroviral initiation rates over the past year, and while further improvement is needed, a lot of this process has been driven by rural programmes.

In addition, KZN has implemented several multidrug-resistant TB treatment programmes that use community-based resources and do not rely on unpopular, expensive and dangerous hospital models. KZN doctors, through simple curiosity and focus on patient outcomes, were the ones who found

the extensively drug-resistant (XDR-TB) outbreak at Tugela Ferry, with subsequent international attention and a welcome shot in the arm for TB programmes and infection control.

The Pfaff/Blaylock issue raises the whole issue of 'dual loyalties'. Is our primary loyalty to our employers, or to the care of our patients? The doctors provided improved care to the most rural community, using evidence-based medicine and no additional resources. Their employer provided obstruction, mixed messages, missed deadlines, and resorted to personal attacks. It was never a contest.

A new political administration looms in South Africa. Maybe now we can get on with improving our buckling health care system, with inspired political leadership. After the past few years, we all deserve it.

FRANCOIS VENTER

President

DEBATE

HIV TESTING AND ARV PROPHYLAXIS FOR NEWBORNS WITHOUT THEIR MOTHERS' CONSENT

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Criminal law, constitutional rights and medical ethics (not forgetting common sense) can at times contradict each other, putting medical professionals on the spot. This article is based on a case study discussed on the *HIV Policy & Ethics Discussion Forum:* http://groups.google.com/group/policy-ethics.

CASE STUDY

A paediatrician is called to the nursery ward of a government hospital to see a male infant born 8 hours previously. The infant's mother is 33 years old, wasted and has oral thrush. This is her second child, the first having died in infancy after a short illness with a history typical of pneumonia.

The mother was not offered an HIV test during pregnancy as the clinic she attended did not have such services. A nurse calls the paediatrician as her offer of HIV testing to the mother has been declined. She requests the paediatrician to convince the woman to test, given the benefits that such knowledge gives the woman, as well as to enable the provision of post-exposure prophylaxis for the newborn and of infant feeding counselling. The paediatrician examines the newborn, who is vigorous, fully grown for age and has no signs of HIV infection. She then carefully counsels the patient, explaining the potential harm of testing, and the benefits of HIV testing, for the woman and her infant. The woman still declines.

The paediatrician is aware of the efficacy of antiretroviral (ARV) prophylaxis given to HIV-exposed newborns whose mothers did not receive ARVs.[1-3] The former's conscience and medical duty to act in the best interests of her patient (the child) have to be balanced against hospital and international policies which state that newborns cannot be tested for HIV exposure and be given prophylaxis without their mothers' consent. She thinks of many other colleagues – such as the previous medical superintendent of the East London Hospital Complex[4] – who in similar situations acted from their conscience, even if such actions were contrary to prevailing policies and protocol. The paediatrician then tests the infant, whose antibody rapid tests show he is HIV-exposed. The doctor provides ARV prophylaxis to the infant, counsels the woman about her own HIV status and enrols her in an HIV clinic which provides antiretroviral treatment (ART).

Questions for discussion

1. Was the paediatrician correct to test the infant without the mother's consent? What is the optimal balance between a woman's right to autonomy and choice, and her infant's access to health care services?
2. Was the paediatrician correct to provide ARV prophylaxis to the infant without consulting the mother? Should the paediatrician have informed her that she had given the infant ARV prophylaxis?

DISCUSSION

AN ETHICAL AND RIGHTS-BASED APPROACH

A woman's constitutional rights to privacy, reproductive choice and bodily autonomy are all too often violated and require adequate legal protection. Also, a woman's right (and legal obligation) to make choices for her child is common practice. However, HIV infection in infants and its concomitant cost and suffering are essentially preventable. In such circumstances, rights compete and need to be carefully weighed. Dedicated efforts, which are culturally appropriate and, ideally, communicated in patients' home language, are needed to explore and address the underlying reasons why the woman declined HIV testing. In South Africa, ART is becoming increasingly available, and systems are in place to safeguard confidentiality. In such settings, it is difficult to construct a reason for not testing an infant; when the mother refuses, that is more compelling than an HIV-free child.

This does not discount the fear of knowing one is HIV infected, nor the potential for violence following disclosure of HIV status to one's partner.

Mandatory testing of newborns could signify the beginning of a slippery slope, potentially eroding the right to refuse testing in situations such as pregnancy, post-rape, pre-marriage, post-occupational injury, or even among couples in general.[5] In itself, a desire not to engage in a 'slippery slope' argument is an inadequate rationale for not choosing between the child's best interests (identifying exposure and receiving ARV post-exposure prophylaxis) and a woman's interests in not knowing her own HIV status. Although legislation,[6] policy,[7] and guidelines[8] emphasise the principle of informed consent, the Constitution trumps these. Section 28 of the Constitution states: 'A child's best interests are of paramount importance in every matter concerning the child.' This clause has been used to assert children's best interests, as in cases where Jehovah's Witnesses declined blood transfusions for their children.[9]

Where current practice conflicts with the child's interests, can health care workers act from their conscience, or is this the sole domain of the courts? Where policy and legislation are outdated and lag behind medical progress, bringing a test case to court could precipitate change. For example, in circumstances where a woman refuses HIV testing after birth, a health care worker could launch an urgent court application to test the infant and provide prophylaxis without the woman's consent. The authors feel that the matter of a paediatrician launching such a case is long overdue. It could be argued that paediatricians each day make active decisions not to test newborns for HIV exposure, even though testing may be in the best interests of those whom they serve.

Several states in the USA have for almost a decade successfully implemented mandatory testing of newborns and thus provided proof of concept and encouraging safety data; this should justify further investigation in the South African context.[10] The state must assume ultimate responsibility for protecting children's health and wellbeing, and should intervene when these are undermined. Another consideration is that children who have contracted HIV could in time argue that, by not having been tested for HIV exposure at birth, the health providers who cared for them after childbirth neglected to protect them from HIV infection and did not act in their best interests.

LEGAL IMPLICATIONS

In the above scenario, it is doubtful that the woman would institute legal action against the pediatrician; but if she were to do so, the legal ramifications for this case study would be essentially threefold:

1. Any invasive medical treatment or test without the patient's consent (in this instance, that of the legal guardian of the infant – her mother) constitutes an assault under South African common law as well as an invasion of personal rights.[11,12]
2. It therefore follows that the mother could lay a charge of assault on behalf of her child against the doctor who tested and provided medical treatment to the infant without the mother's consent.
3. The mother would also be in a position to report the paediatrician to the Health Professions Council of South Africa (HPCSA) for unethical conduct.

However, it is unlikely that such a course of action would succeed in court. In her defence, the paediatrician would be able to argue that the court is under a constitutional obligation to develop common law so as to '... promote the spirit, purport and objects of the Bill of Rights' (section 39(2) of the Constitution) and in line with the paramount place given to the interests of the child (section 28(2) of the Constitution).

Evidence is overwhelming that it is not in the best interests of a child to acquire HIV from the mother, and that providing HIV testing and post-exposure prophylaxis will reduce the risk of the child contracting a chronic and life-threatening illness. Moreover, medical evidence shows that administering a single dose of ARVs to an infant is not harmful.[13]

The paediatrician could therefore argue that courts are constitutionally obliged to develop the common law of assault to exclude instances of beneficent intervention in the interests of a minor. With this approach, it is likely that the doctor would be acquitted of a charge of assault, while the Health Professions Council would probably make a similar finding.

CONCLUSION

A test case may effect policy change, though must never negate or minimise the real difficulties that women face in this epidemic, and their needs for care and support. Ideally, women should be strongly encouraged to test and be referred to appropriate programmes during or prior to pregnancy. In lieu of this, the infant's interests in not contracting HIV are paramount.

Perhaps the epidemic could be reversed with more vigorous interventions, carefully considered and with specific efforts to minimise any human rights infringements. Where access to HIV treatment and confidentiality are assured, the degree and range of benefits of an early HIV diagnosis differ markedly from those of a late diagnosis when HIV inevitably declares itself with severe diseases. Perhaps health workers have for too long protected people from facing an inevitable diagnosis, rather than protecting adults' health and that of their children. We can never turn back the clock, but we can alter the speed of its ticking.

REFERENCES

1. Gray GE, Urban M, Chersich MF, *et al.* A randomized trial of two postexposure prophylaxis regimens to reduce mother-to-child HIV-1 transmission in infants of untreated mothers. *AIDS* 2005; 19(12): 1289-1297.
2. Wade NA, Birkhead GS, Warren BL, *et al.* Abbreviated regimens of zidovudine prophylaxis and perinatal transmission of the human immunodeficiency virus. *N Engl J Med* 1998; 339(20): 1409-1414.
3. Taha TE, Kumwenda NI, Hoover DR, *et al.* Nevirapine and zidovudine at birth to reduce perinatal transmission of HIV in an African setting: a randomized controlled trial. *JAMA* 2004; 292: 202-209.
4. Ndou C. Doc who supported Nozizwe suspended. *Mail & Guardian* 2007; 14 August.
5. Venter FW. Make HIV tests compulsory for South Africans. *Sunday Times* 2007; 3 June.
6. *The National Health Act, 2003.* Pretoria: Government Printer, 2005.
7. *National Policy on Testing, 2000.* Pretoria: Department of Health, 2000.
8. *The Management of Patients with HIV Infection or AIDS.* Pretoria: Health Professions Council of South Africa, 2007.
9. Venter Z. Doctors go to court to get blood for baby. *IOL* 2005; 25 October.
10. Susman E. Despite the controversy, HIV prenatal testing laws get the job done. *AIDS* 2001; 15(14): N15-16.
11. Stoffberg v. Elliott 1923 CPD 148.
12. Castell v. De Greef 1994 (4) SA 408 (C).
13. Mofenson LM, Munderi P. Safety of antiretroviral prophylaxis of perinatal transmission for HIV-infected pregnant women and their infants. *J Acquir Immune Defic Syndr* 2002; 30(2): 200-215.

REBUTTAL

COERCIVE POLICIES DO NOT MAKE FOR BETTER HEALTH OUTCOMES

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As it stands, this argument for mandatory newborn testing unnecessarily pits the interest of mother and child against each other and creates conflict where there should be collaboration. Our main concern is that it fails to acknowledge the consequences of the fact that newborn testing amounts to 'proxy testing' of the mother – in this case, without her consent. Not only do the paediatrician's actions violate the mother's right (and indeed legal obligation) to make medical decisions for her minor infant, they also violate her constitutional rights to privacy, reproductive choice and bodily and psychological integrity.[1] The policy change that Chersich and Richter are urging would disempower and undermine women's agency on a number of levels. Further, proxy testing of the mother in this way is a violation of fundamental rights that are now recognised and widely accepted as necessary components of ethical HIV diagnosis and treatment. These include the right to informed consent and not to be tested against one's will. Such rights are enshrined in both national and international policy, guidelines and legislation[2,3] and – perhaps most importantly – the South African HIV & AIDS and STI National Strategic Plan 2007 - 2011.[4] They are also recognised internationally as good public health practice by WHO and UNAIDS.[5,6]

The authors admit that mandatory testing could prompt an 'eroding [of] the right to refuse testing in [other] situations'. Yet they seem reluctant to fully engage with this danger. The acts of testing and administering medication to an infant without its mother's consent are but a small step away from forcing all pregnant women to test for HIV, and if they test positive, to compel them to take nevirapine or AZT before they give birth. Indeed, some bioethicists are already making this argument.[7] But further dangers lurk on this slippery slope. Ignoring the mother's rights and autonomy in the name of acting 'in the best interests of the child' raises the spectre of a much more severe monitoring of pregnant women lest the infant suffer harm (e.g. ensuring that they do not smoke, use alcohol and drugs, or exercise too vigorously). Such 'monitoring' would erode decades of progress made in the field of women's reproductive health and rights. It would also take us back to an earlier era in which women were regarded as little more than conduits for healthy babies.

Although we agree that more culturally sensitive efforts are needed to better understand the reasons why women in such situations may decline testing, much of this is already known. There has been extensive social science research on stigma, denial and blame in the epidemic – and on the role that gender plays in the particular configurations of these collective responses.[8-11] We also know from studies of HIV disclosure, for example, that the diagnosis itself is still received by many with profound dread. Suicide ideation following a positive diagnosis is common.[12] But it remains the case that women, in particular, bear the brunt of this stigma: they are often blamed for bringing HIV into the home or into a relationship, they face the very real danger of being beaten by an abusive partner, abandoned, shunned, ejected from the home and rendered destitute.[13-15] These are not uncommon consequences of the abjection that HIV continues to signal for many people, and which makes an HIV diagnosis something to fear and avoid, both for the individual concerned and for the wider community in which they live. Notwithstanding the limited gains made in reducing stigma in recent years, we should not mandate proxy HIV testing for women unless these issues have been more fully addressed.

The woman in the case study cited above may be faced with further challenges. Her own health seems precarious and after giving birth, she might not have had the emotional or physical resources to cope with a positive HIV diagnosis, much less to deal with the implications of her child receiving antiretroviral prophylaxis. Under such circumstances, what chance does the health of the infant have? With no acknowledgement of the known relationship of infant survival to its mother's wellbeing and survival, the debate is reduced to a simplistic contest between mother and baby. Yet a newborn does not exist in a vacuum; the mother's health and wellbeing are central to efforts to improve infant health.[16-18] Furthermore, the paediatrician may have conflicting moral obligations

between baby and mother, but the hospital itself has an obligation to *both* the mother and the baby. One cannot be ignored at the expense of the other.

This raises a further concern for us. The case study notes that 'the mother was not offered an HIV test during pregnancy as the clinic she attended did not have such services'. This suggests that the problems need to be addressed upstream, with a particular focus on prongs 1 and 2 of the World Health Organization prevention of mother-to-child transmission (PMTCT) strategy.[19] Thus the first points of intervention would be: helping women in high prevalence regions to assess their own risk of infection, empowering them with knowledge to protect themselves, preventing unintended pregnancy in women with HIV, and making safe abortion readily available. Then we would need to ensure that all antenatal clinics *do* have VCT services – and that the quality of counselling and follow-up support is high, so that more women choose to be tested during pregnancy and enter PMTCT programmes if necessary. Community-based interventions, in particular 'mother-to-mother' support groups or one-on-one counselling, are powerful and effective.[20,21] We suspect that the woman in the case study might have responded differently if she had been counselled by a peer who shared her language and cultural background, and who had perhaps been through similar experiences herself. This would have been preferable to being 'convinced' to test in a time of stress where informed consent could not be assured and thus was ignored by a paediatrician whose main concern was clearly the health of the infant. Moreover, consent is important not only from a human rights perspective but also from a medical point of view: when people's choices are disregarded and when their buy-in is not secured, treatment and follow-up may be compromised. Bringing a test case to court could potentially undermine precisely the purpose it is meant to serve, namely protecting the health of infants. It could also have longer-term public health consequences, since this kind of legal action could deter vulnerable women from seeking out antenatal care at all. The policy and legislative changes proposed by the authors, we argue, are premature if not completely unnecessary.

The authors posit that '[p]erhaps the epidemic could be reversed with more vigorous interventions ...'. We agree that the severity of the South African epidemic calls for firm and decisive intervention. But we should not forget that an estimated 85% of HIV in this country is transmitted through heterosexual intercourse.[4] Recall that the policy of mandatory newborn testing is intended to address the category of women who don't know their HIV status at time of giving birth yet refuse testing, both for themselves and for their infant. In turn, it is presumed that this policy would ultimately ensure that mother-to-child transmission is virtually eliminated. But in reality the numbers of women who fall into this category (of refusals) is likely to be very small. Indeed, there is evidence that with high-quality counselling, uptake of VCT among women in antenatal settings is very high.[22,23] In fact, this vital information is central to the debate – yet the authors make no mention of it. Why, then, the need for a measure as coercive as mandatory newborn testing, enforced by law and policy, when the overall impact of this intervention on the HIV epidemic is likely to be relatively negligible?

Finally, for the authors to invoke the argument about health care workers' conscience is to assume that decisions made from 'conscience' will, in every case, align with what is *medically* the best decision to make for the patient. But this surely cannot be the case. We have only to consider a comparable situation relating to the implementation of termination of pregnancy policy in South African public health facilities. Here, too, we find health workers acting on the grounds of 'conscience' and refusing to have any part in carrying out the procedure. But many of these health workers also refuse to arrange adequate counselling or referral for the women concerned. Acts of 'conscience' are admirable, indeed. But they are hardly neutral, objective or necessarily medically correct.

In conclusion, we regard this argument as a classic example of 'act first, think later'; a narrow, biomedical and legal solution to a complex human problem. We are a long way from ensuring quality services for HIV-positive women and protecting their rights to information, privacy and confidentiality. Our view is that women should not have to pay for the failures of primary HIV prevention and reproductive health services, nor should their rights be sacrificed because political commitment and leadership in the epidemic has been lacking. In short, more debate is needed – and we would urge that such debate involves a wide range of stakeholders: not only maternal and child health specialists and bioethicists, but also experts and advocates in the fields of women's reproductive health and rights, AIDS activists, civil society organisations, social scientists, and representatives of government. Most importantly of all, we need to hear the voices of ordinary women in South Africa who are actually confronted with such painful dilemmas every day.

REFERENCES

1. South African Constitution, 1996. Chapter 2 (Bill of Rights), sub-sections 12 and 14.
2. Health Professions Council of South Africa. Guidelines for the management of patients with HIV infection or AIDS; 2002. http://www.hpcsa.co.za/hpcsa/UserFiles/File/Booklets/Booklet%208%20HIV.pdf (accessed 14 April 2008).
3. South African Department of Health. Draft national policy on testing for HIV; 1990. http://www.doh.gov.za/aids/docs/policy.html (accessed 14 April 2008).
4. The HIV & AIDS and STI strategic plan for South Africa (NSP 2007-2011); 2007. http://70.84.171.10/~etools/doh/strat-plan/hiv-aids1.pdf (accessed 14 April 2008).
5. Jurgens R. *Increasing Access to HIV Testing and Counseling While Respecting Human Hights*. Background paper. New York: Public Health Program of the Open Society Institute, 2007.
6. UNAIDS, WHO. UNAIDS/WHO Policy Statement on HIV Testing; 2004. http://www.who.int/hiv/pub/vct/en/hivtestingpolicy04.pdf (accessed 14 April 2008).
7. Schuklenk U, Kleinsmidt A. Rethinking mandatory HIV testing during pregnancy in areas with high HIV prevalence rates: ethical and policy issues. *Am J Public Health*

2007; 97(7): 1179-1183.
8. Campbell C, Nair Y, Maimane S. AIDS, stigma, sexual moralities and the policing of women and youth in South Africa. *Feminist Review* 2006; 83: 132-138.
9. Delius P, Glaser C. Sex, disease and stigma in South Africa: historical perspectives. *African Journal of AIDS Research* 2005; 4(1): 29-36.
10. Lawless S, Kippax S, Crawford J. Dirty, diseased and undeserving: the positioning of HIV positive women. *Soc Sci Med* Nov 1996; 43(9): 1371-1377.
11. Skinner D, Mfecane S. Stigma, discrimination and the implications for people living with HIV/AIDS in South Africa. *Journal of Social Aspects of HIV/AIDS* 2004; 1(3): 156-164.
12. Squire C. *HIV in South Africa: Talking about 'the big thing'.* London and New York: Routledge, 2007.
13. Dunkle KL, Jewkes RK, Brown HC, Gray GE, McIntryre JA, Harlow SD. Gender-based violence, relationship power, and risk of HIV infection in women attending antenatal clinics in South Africa. *Lancet* 2004; 363(9419): 1415-1421.
14. Dunkle KL, Jewkes RK, Brown HC, *et al.* Prevalence and patterns of gender-based violence and revictimization among women attending antenatal clinics in Soweto, South Africa. *Am J Epidemiol* 2004; 160(3): 230-239.
15. Vetten L, Bhana K. Violence, vengeance and gender. A preliminary investigation into the links between violence against women and HIV / AIDS in South Africa. Johannesburg: Centre for the Study of Violence and Reconciliation, 2001.
16. Nakiyingi JS, Bracher M, Whitworth JA, *et al.* Child survival in relation to mother's HIV infection and survival: evidence from a Ugandan cohort study. *Aids* 2003; 17(12): 1827-1834.
17. Newell ML, Brahmbhatt H, Ghys PD. Child mortality and HIV infection in Africa: a review. *Aids* 2004; 18: Suppl 2, S27-34.
18. Newell ML, Coovadia H, Cortina-Borja M, Rollins N, Gaillard P, Dabis F. Mortality of infected and uninfected infants born to HIV-infected mothers in Africa: a pooled analysis. *Lancet* 2004; 364: 1236-1243.
19. WHO. Strategic approaches to the prevention of HIV infection in infants: report of a WHO meeting, Morges, Switzerland, 20-22 March 2002. http://www.who.int/hiv/pub/mtct/en/StrategicApproachesE.pdf (accessed 5 September 2007).
20. mothers2mothers. http://www.m2m.org/ (accessed 14 April 2008).
21. Coetzee D, Hilderbrand K, Boulle A, Draper B, Abdullah F, Goemaere E. Effectiveness of the first district-wide programme for the prevention of mother-to-child transmission of HIV in South Africa. *Bull World Health Organ* 2005; 83(7): 489-494.
22. Centers for Disease Control and Prevention. Introduction of routine HIV testing in prenatal care – Botswana, 2004. *MMWR Morb Mortal Wkly Rep* 2004; 53(46): 1083-1086.
23. Urban M, Chersich M. Acceptability and utilisation of voluntary HIV testing and nevirapine to reduce mother-to-child transmission of HIV-1 integrated into routine clinical care. *S Afr Med J* 2004; 94(5): 362-366.

OPINION

IN DEFENCE OF RATIONAL AIDS ACTIVISM

How the irrationality of Act Up-Paris and others is risking the health of people with HIV or at risk of HIV infection

Nathan Geffen, Gregg Gonsalves

This article describes the irrational actions of Act Up-Paris and some other organisations in recent years. We have written it because their activities are threatening the development of new treatment and prevention technologies for people with HIV. They are also undermining scientific research programmes in developing countries.

The groups we discuss here couch their anti-science agenda in progressive rhetoric. They therefore persuade some well-intentioned people and organisations unfamiliar with HIV science to support their causes. But there is nothing progressive about hindering life-saving medical research. Act Up-Paris and the other organisations discussed here are endangering the lives of people with HIV; they have to be exposed.

THE SUCCESSES OF AIDS ACTIVISM

AIDS activists have led the struggle against HIV via successful campaigns for lower medicine prices, public sector programmes and increased international funding for HIV programmes. By sharing their skills and knowledge with each other – through informal networks of collaboration, training, publications and web-based information – AIDS activists have been the drivers of community health education programmes across the globe. Their efforts have enabled poor people in Africa, Eastern Europe, South America, the Caribbean and Asia to become community educators and more effective activists themselves. There is now a strong and vital global movement of AIDS treatment activists that has revolutionised how science is conducted, how health care is delivered, and how health care workers relate to their patients.

Community involvement in drug development and AIDS research has depended on the willingness of scientists to assist activists in learning the science of HIV/AIDS. This *ad hoc* scientific education has been critical in lifting community involvement beyond the tokenism of identity politics. Because people living with HIV – including women, gay men, drug users and people of colour – have learned the science of HIV/AIDS, they can engage with experts at the US National Institutes of Health (NIH), the US Food and Drug Administration (FDA), the World Health Organization (WHO) and other institutions on scientific issues, and offer a perspective grounded on sound evidence-based principles and methodology.

These are just some of the successes activists have helped to secure over the past 27 years. Despite these advances, many opportunities have still been lost: far too few people receive the treatment and prevention interventions they need, and all too often ideology has trumped science in delivering these services causing millions of avoidable new infections and deaths. But the global response to the epidemic would have been far worse without activism, with even more devastating consequences.

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THE RISE AND FALL OF RATIONALISM IN ACT UP-PARIS

Yet there are some AIDS activists whose actions and campaigns are counter-productive, even dangerous. Of course, every major activist group makes serious mistakes from time to time, be they factual, tactical or even ethical lapses. But some activist groups, in particular Act Up-Paris, have developed a pattern of irrational behaviour.

The organisation has in recent years actively worked to undermine cutting-edge life-saving HIV clinical research in Africa. Act Up-Paris used to be an effective activist group. In its earlier years under the leadership of Didier Lestrade and others, it worked closely with other groups in North America and Europe to forge the first relationships between activists and researchers. It made significant contributions to clinical trials and drug approval in Europe.

But in recent years the organisation has been taken over by new leadership that lacks a rigorous knowledge of HIV science and clinical trials and an understanding of the needs of people with HIV or at risk of infection in developing countries, or the nuances of modern political struggle outside of France. In particular, over the past few years, Act Up-Paris has targeted several clinical trials in developing countries as unethical without evidence to support their claims.

HOW ACT UP-PARIS SHUT DOWN TENOFOVIR TRIAL SITES

In 2004 - 2005, Act Up-Paris actions led to the shutting down of clinical trial sites examining pre-exposure prophylaxis with tenofovir in several countries around the world. The controversy over the tenofovir studies is complex, but throughout this period Act Up-Paris sought to exacerbate tensions between researchers and community groups rather than look for solutions that would have allowed these critical studies to continue.

The controversy essentially began as a local issue between researchers from the USA and Australia and an organisation representing sex workers in Cambodia, with the local NGO claiming they had not been consulted in the preparations for the study nor received sufficient assurances that sex workers infected during the course of the study would have access to health care for their HIV infection.

The issue of post-trial care for clinical trials is a key one, but the solution is difficult and in this case needed lengthy discussion among stakeholders in Cambodia about how to address it. For instance, since people infected during the study would probably not get sick and need treatment for a decade, how would care that would be needed years in the future be assured? What is the responsibility of the local health system to provide AIDS treatment to all its citizens, not just clinical trial participants?

However, instead of attempting to deal constructively with these issues, Act Up-Paris led demonstrations at the International AIDS Conference in Bangkok in 2004 accusing Gilead, the manufacturers of tenofovir (which had no involvement with the study), and the study investigators of unethical conduct.

In addition, Act Up-Paris through its networks in francophone Africa flamed controversy about another tenofovir study being planned in Cameroon. A local Cameroon group and Act Up-Paris charged that inadequate counselling had been provided to trial participants, though at a meeting on the tenofovir studies in Seattle in 2005 neither group could adequately describe the deficiencies in the counselling protocol or its implementation and the description offered was contradicted by others involved with the study.

The tenofovir trials raised a host of issues around the conduct of clinical trials in developing countries, including post-trial care, informed consent, counselling of trial participants, the availability of other prevention interventions for participants in both control and experimental arms of the studies, and community involvement in study design and conduct. These issues are relevant to all HIV prevention research trials and, in part, clinical research overall in developing countries. However, what is needed to move the dialogue on the conduct of clinical trials forward in developing countries is an evidence-based, methodical and rational discussion of all these operational considerations. The difficulty in addressing these issues means there are no easy answers; partnership between all stakeholders is needed to resolve them. Though there were real issues around the tenofovir studies, Act Up-Paris sought to inflame the debate, was cavalier in offering evidence of wrong-doing, and often demanded impractical solutions to key issues.

With the closure of several of the tenofovir studies, it became difficult to ascertain the effectiveness of this potentially important new tool in HIV prevention, as the statistical power of the remaining studies was too weak to offer a reliable answer to the question. Act Up-Paris is responsible for this delay in answering a critical question in AIDS research, one that could potentially lead to a new intervention preventing millions of new HIV infections.

HOW ACT UP-PARIS TRIED TO DISCREDIT A HIGHLY SUCCESSFUL AFRICAN TRIAL

In 2006, Act Up-Paris attempted to discredit the DART trial. This trial, sponsored by the British Medical Research Council, took place in Uganda and Zimbabwe. It examined two questions: whether antiretrovirals can be administered in the absence of routine laboratory tests, and whether patients can take structured treatment interruptions.[1] The idea of treatment interruptions was to reduce side-effects and the inconvenience of having to take pills daily for life. It would also reduce costs. Unfortunately, structured treatment interruptions do not work; they increase the risk of morbidity and mortality. DART was one of three major trials that showed this, though it found a statistically significant effect for morbidity, not mortality (2 per 100 patient-years versus 8.6 per 100 patient-years).

Act Up-Paris's response was to accuse the DART investigators of endangering the lives of trial participants who were interrupting treatment and to disrupt the speech of one of the DART researchers, James Hakim, a Zimbabwean researcher, given at the 2006 International AIDS Conference in Toronto. They shouted during Hakim's speech and held up banners saying shame. They also distributed a pamphlet making a series of false allegations about the ethics and science of the trial. When they finished their demonstration one of the DART scientists, Paula Munderi, presented data showing 94% survival at 2 years and a 17-fold reduction in mortality compared with pre-antiretroviral data in this cohort. Unfortunately the Act Up-Paris demonstrators had left before Munderi spoke.

Participants in the DART trial, on all arms, actually did remarkably well. The trial has provided yet another example of how antiretroviral treatment can be implemented successfully in poor-resource settings. Although the trial found that patients in the structured treatment interruption arm had more serious adverse events, the interruptions were terminated once this was determined and all patients were put on continuous therapy. Three patients died out of 137 (2.4%) in an initial structured treatment interruption pilot. In two arms – consisting of a total of 813 patients – comparing continuous treatment versus structured interruptions, 9 patients died, 5 from the interruption arm and 4 from the continuous arm. The death rates in both arms of the study are low and when compared with high mortality in the general population living with HIV in both Uganda and Zimbabwe, show a strong benefit for antiretroviral therapy overall. [2,3]

No evidence has been brought forward to support Act Up-Paris's claims that there was inadequate consent or that patients were not given appropriate support and care. TAC wrote a letter to Act Up-Paris pointing out the errors in some of their allegations. We asked them to either provide evidence to support their claims or to apologise and withdraw them. Act Up-Paris responded defensively, repeating many of their earlier claims but producing no evidence.[4*]

SOMO'S ATTEMPT TO DISCREDIT HIVNET 012

Another European activist organisation making irrational claims about HIV science is the Dutch-based Centre for Research on Multinational Corporations (Stichting Onderzoek Multinationale Ondernemingen – SOMO). It published a briefing on what the organisation calls examples of unethical clinical trials.[5] We are only familiar with three trials in the list. No rational activist would hold these up as unethical, at least not for the reasons cited by SOMO. Two are the tenofovir and DART trials discussed above, and SOMO's attacks are largely based on the critique launched against these studies by Act Up-Paris. The third is the HIVNET 012 trial that took place in Uganda, which readers of this journal will know found that a single dose of nevirapine to mother and child reduces the risk of mother-to-child transmission of HIV by about half. The aim of the trial was to find a simple, affordable method of reducing paediatric HIV infections that could be implemented easily in poor countries.

The controversy surrounding HIVNET 012 has been widely reported in both the popular and scientific press. Initially, in December 2004, John Solomon of the Associated Press (who has recently become editor of the right-wing *Washington Times*) erroneously reported that there had been serious irregularities in the study, which took place in the late 1990s. These false charges became exaggerated in the media, with some commentators comparing the HIVNET 012 study to the infamous Tuskegee experiment that deprived African-American men of a proven cure for syphilis in a study conducted in the United States between 1932 and 1972.[6] Since 2004, these claims have been used by pseudo-scientists who deny the link between HIV and AIDS to undermine the provision of nevirapine in South Africa and elsewhere.

It was certainly not a perfect trial; indeed, a perfectly conducted clinical trial is extremely rare. Also, it has been criticised – notably by former *New England Journal of Medicine* editor Marcia Angell and respected consumer rights activist Ralph Nader's organisation, Public Citizen – for having had a placebo arm when it was already known that AZT was effective at reducing transmission.[7] Consequently the trial protocol was changed so that the control group used a very short-course AZT regimen instead of placebo. The fact that this regimen was shorter than the AZT intervention known to work is a legitimate criticism of HIVNET 012. But it was one that was debated openly in which reasonable arguments were put forward by both sides. Furthermore, the trial protocol was approved by an ethics committee.

However, this is not the criticism that has made HIVNET 012 the subject of intense media attention, nor is it the one highlighted by SOMO. Instead SOMO reports several partly true minor allegations about the trial and several major untruths including that 14 deaths went unreported.[†] The only references they provide for their allegations are the inaccurate Associated Press articles by John Solomon, not independent reviews or scientific papers.

*Act Up-Paris claimed to receive information about their allegations from a trial participant. Yet this person failed to attend a meeting with the researchers to discuss his concerns nor does the name he has used correspond with anyone on the trial.

[†]The independent review of HIVNET 012 conducted by the Institute of Medicines states 'In its review of HIVNET 012 records, the committee finds no evidence of and only a very limited opportunity for either unreported deaths or erroneous reports of deaths.'

Unmentioned in the SOMO report is that the HIVNET 012 trial has been evaluated several times for ethical and scientific lapses. It has never been found by any of these reviews to have made a serious ethical breach. The US Institute of Medicine conducted an independent review of HIVNET 012. The chair of the investigating panel described their findings: 'The data from the HIVNET 012 study ... are sound and reliable. ... Our confidence in the trial's data and findings is based on several factors, including evidence that the study's design was both scientifically sound and *ethically implemented* [our emphasis].[8]

Interestingly, omitted from SOMO's long list of unethical trials is one of the worst such cases. Matthias Rath is an entrepreneur who has established multinational vitamin-selling operations. He has made a fortune selling his products at exorbitant prices by claiming, falsely, that vitamin supplements treat almost every serious disease including asthma, heart attacks, AIDS and, more recently, bird flu. With the implicit support of South Africa's Minister of Health and Director-General of Health, he ran an unauthorised illegal clinical trial in Cape Town. There are a myriad of ethical problems with the trial and several deaths have been documented. The evidence is public and yet Rath has not been prosecuted, or even stopped.[9]

SOMO, if it was genuinely interested in stopping unethical trials, could make a difference in the effort to stop Rath. This is because he runs his European operations in Holland. A systematic campaign against Rath might have been of tremendous assistance in our efforts in South Africa to bring Rath to justice.

Maybe the motives behind the irrational behaviour of organisations like SOMO and Act Up-Paris can be understood by SOMO's failure to mention Rath's trial. Science writer Jon Cohen has written about what he terms pharmanoia, the irrational fear and/or hatred of pharmaceutical companies and their products: 'The protest against Gilead is one example of pharmanoia, the extreme distrust of drug research and development that's sweeping the world. ... By overplaying unproved but sensational misdeeds, Big Pharma's watchdogs obscure serious ones – like the inane lawsuit that 39 drug makers filed against the South African government in 1998 to block it from making generic versions of anti-HIV drugs. The scattershot approach also draws attention away from a critical and increasingly complicated issue that AIDS has pushed to the fore ...'[10]

There is a view, with some justification, that pharmaceutical companies conspire with Western governments to protect their business interests, even at the expense of patients. SOMO, Act Up-Paris and the other organisations discussed here have taken this view to an ideological extreme, in which the actions of pharmaceutical companies and HIV clinicians are always presumed to be unethical, irrespective of the evidence. Consequently, these organisations are unable to evaluate facts that do not fit into this world-view. The actions of an alternative medicine seller, Matthias Rath, who ran a deadly trial in cahoots with a developing country government, do not fit neatly into this ideology and are therefore ignored.

HOW SEVERAL ORGANISATIONS ARE TRYING TO DERAIL A CIRCUMCISION PROJECT

Less known than the irrational attacks on the tenofovir trials, HIVNET 012 and DART, is the attempt by Act Up-Paris and several other organisations to derail an important prevention study in Orange Farm, Johannesburg.

Following the successful Orange Farm circumcision trial, the lead researcher Bertran Auvert rightly believes that he has a duty to follow up the trial by making circumcision widely available to the community. After all, the Orange Farm community helped show that circumcision reduces HIV transmission. Surely the community should be given the opportunity to benefit from it. Few uncircumcised Orange Farm men could afford to pay for their circumcisions, so Auvert applied to ANRS to fund a community study of male circumcision.

It is a 5-year programme that, in its first 2 years, will offer circumcision to about 20 000 uncircumcised men aged 18 - 39. The study protocol includes counselling and the offer of HIV testing. Patients with HIV will be referred to Orange Farm's clinic, which provides antiretrovirals. Critically, it will help answer some outstanding operational questions about circumcision.

The researchers will evaluate impact on the community's knowledge and attitudes. It will support existing means of prevention such as sexual behaviour change, condom use, sexually transmitted infection behaviour and voluntary counselling and testing, and the spread of HIV and the herpesvirus (taken from the project proposal).

Four French activist organisations, Act Up-Paris, Aides, Sidaction and TRT-5, have written a letter to ANRS attacking the trial protocol and attempting to stop it. The letter's header, in large capital letters, states 'WARNING TO THE DIRECTOR OF THE ANRS REGARDING THE PLANNED ANRS TRIAL 12126' (we have a professional translation of the original letter, which was written in French).

The writers describe themselves as a 'task group' that 'opposes the setting up of the study in its current form'. They make a series of false claims. For example, they claim the intervention is not 'part of a complete set of HIV prevention measures' which should include 'advice,

access to testing, treatment of sexually transmitted infections, promotion of safe sex, easy access to male and female condoms, promotion of their proper and regular use'.

But on the contrary, the study protocol includes voluntary counselling and testing for participants and counselling on sexually transmitted infections and safer sex. Symptomatic sexually transmitted infections will be treated. The project will work with the health facilities in Orange Farm and ensure that participants who test HIV-positive will get antiretroviral treatment if indicated.

Act Up-Paris *et al.* claimed there was a lack of clarity regarding the approach to the South African ethics committee. It's not clear what they meant, but the protocol has been approved by the Wits University's ethics committee.

They also claimed that local organisations and authorities had not been consulted. This is despite the researchers working, for many years now, with groups in Orange Farm. They have also consulted with TAC, AIDS Consortium and provincial government officials.

Act Up-Paris *et al.* also claimed that there was virtually no local collaboration with South African social scientists. Yet one of the lead investigators is Dirk Taljaard, a South African social scientist who was an investigator in the previous circumcision study in Orange Farm.

Even if any of the above allegations were valid, surely the correct approach would have been for Act Up-Paris *et al.* to write a very different style of letter to the researchers and ANRS, one that recommended improvements. Instead, they wrote their complaint months before the project was scheduled to start without first giving the investigators an opportunity to address their concerns.

ATTACKS ON THE NONOXYNOL-9 RESEARCHERS

One of the signatories of the letter to ANRS denouncing the circumcision study is Marie de Cenival of Sidaction. She has been centrally involved in Act Up-Paris for many years. Her irrational actions are particularly concerning. In July 2007, at a conference on women and AIDS in Nairobi, she stood up during a session on a panel discussion on microbicides and accused the panel members of killing 900 women. She was referring to a study of a nonoxynol-9 gel (N-9) called the COL-1492 trial. Perhaps, the most bizarre aspect of her allegation is that none of the panellists were investigators on this trial! (Personal communications with scientists and activists in attendance at the Nairobi conference.)

During the study, 59 women became HIV infected out of 892 women on the N-9 gel arm as opposed to 45 new infections in the control arm, where women received a placebo, a gel that did not contain N-9. Consequently the trial was stopped. Obviously a negative result, where the tested product performs worse than placebo, is tragic. Yet the infection rate in the N-9 arm was lower than the background infection rate in the community, possibly because of the counselling and care incorporated into the trial for both sets of women, i.e. those receiving the N-9-containing gel and those receiving a placebo. There was nothing close to 900 deaths. Nonoxynol-9 does not work. This was an unfortunate and unexpected scientific result. But de Cenival's accusation was false.

THE CONSEQUENCES OF IRRATIONAL ACTIVISM

The trials discussed here that irrational activists have attacked were all conducted in developing countries, mainly African, with the involvement of scientists in those countries. Three outstanding African scientists, Peter Mugyenyi, Paula Munderi and James Hakim, played a leading role in the DART study. Conducting high-quality science in Africa, especially outside South Africa, is difficult. Not only do scientists have to contend with a lack of finance, equipment and facilities, they now also have to contend with what amounts to a concerted campaign to unfairly discredit their work.

As TAC's chairperson Zackie Achmat wrote in the prologue to Sipho Mthathi's and his letter to Act Up-Paris, 'Their unsubstantiated hysteria has undermined support for AIDS research and sowed unnecessary fear and suspicion about research among people living with HIV/AIDS across the world.'

Act Up-Paris's actions have done a great disservice to people living with HIV and those at risk of HIV transmission. Our appeals to their leaders to stop their harmful actions have been met by scorn and contempt. There are worrying indications that other organisations, from SOMO in Holland to well-respected French AIDS groups including Aides, Sidaction and TRT-5, are buying into Act Up-Paris's irrational critiques and ideologically driven methodologies – their 'pharmanoia'. We find this a dangerous development in AIDS activism and one which demands that AIDS activists around the world speak up against this trend. It does not give us any pleasure to have to take this step. Both of the authors of this piece have been critics of AIDS research, drug and vaccine and microbicide development for many years. We are not asking for *carte blanche* for researchers to do what they please in our countries. However, our criticisms of clinical research need to be factually sound.

Scientific research is the reason why technology exists that renders HIV infection a chronic lifelong infection, as opposed to the death sentence it used to be. The significant investment into that research and the high quality with which most of it has been conducted are in large part due to the efforts of activism. As activists

we should not allow that success story to be undone by irrational behaviour. The consequences will be deadly.

REFERENCES

1. DART. 2007. Brief Summary. http://www.ctu.mrc.ac.uk/dart/summary.asp (last accessed 6 June 2008).
2. DART. 2007. Structured treatment interruptions (STIs) vs. continuous therapy (CT) in DART. http://www.ctu.mrc.ac.uk/dart/STIsInDART.asp (last accessed 6 June 2008).
3. DART. 2006. DART trial moves patients from interrupted to continuous antiretroviral therapy (ART). http://www.ctu.mrc.ac.uk/dart/files/DARTPressreleaseFINAL14Mar06.pdf (last accessed 6 June 2008).
4. For TAC's letter and Act Up-Paris's response see http://www.lemegalodon.net/a7478-dart-trial-treatment-action-campaign-tac.html (last accessed 6 June 2008).
5. http://www.somo.nl/html/paginas/pdf/Examples_of_unethical_trials_nov_2006_NL.pdf (last accessed 6 June 2008).
6. http://www.aidsnews.org/2004/12/nevirapine-ap.html
7. AIDSTruth. 2006. The HIVNET 012 Trial. http://www.aidstruth.org/hivnet012.php (last accessed 6 June 2008).
8. The HIVNET 012 saga is documented in detail at http://www.aidstruth.org/hivnet012.php (last accessed 6 June 2008) and the links from this page.
9. For details of Rath's dangerous and illegal activities, see www.tac.org.za/rath.html (last accessed 6 June 2008). Also see Geffen N, 2006. *Echoes of Lysenko: State-Sponsored AIDS Pseudo-science in South Africa.*
10. Cohen J. 2006. Pharmanoia coming to a clinical trial near you. http://www.slate.com/id/2136721/ (last accessed 6 June 2008).

GUIDELINES FOR THE PREVENTION AND TREATMENT OF HIV IN ARRESTED, DETAINED AND SENTENCED PERSONS

These guidelines have been developed to aid in the provision of appropriate and quality care for prisoners living with or at risk of HIV infection in detention facilities in southern Africa.

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Anwar Bulbulia received honoraria from Abbott Laboratories and received a research grant from Roche. Eric Hefer owns shares in Calibre Clinical Consultants, received honoraria from Aspen Pharmacare, received research support from MSD and Aspen, and acted as a consultant to Commend (medical schemes), CAMAF, Attran, SAMA and some employer groups. Francois Venter has received travel and/or accommodation support to attend meetings from Gilead, Aspen Pharmacare and Abbott Laboratories.

Jonathan Berger, Natasha Davies, Gary Reubenson, Juno Thomas and Debbie Haines have no conflicts of interest to declare.

Definitions
Some of the terms used in these guidelines may have different legal meanings in different countries. For this reason, these guidelines rely on the following broad definitions, unless the context clearly indicates otherwise:

'Arrest' means take into custody by or on the instruction of any state authority for any alleged offence, including detention without charge or detention for questioning.

'ARV' means antiretroviral medicine.

'ART' means ARV treatment.

'Detention facility' means a state facility – or a facility operated on behalf of the state – where arrested persons are detained, including prisons (correctional centres), police holding cells, refugee holding facilities and juvenile detention centres.

'Health care worker' ('HCW') means a trained professional involved in the provision of health care.

'PEP' means post-exposure prophylaxis for HIV and other sexually acquired conditions.

'Prisoner' means any arrested person.

1. INTRODUCTION

'One of the most unfailing tests of a civilization lies in how a country treats its criminals.'
Winston Churchill

HIV is an everyday reality within southern African detention facilities. Providing prisoners with access to effective and appropriate prevention and treatment services is an essential component for the control of the dual pandemics of tuberculosis (TB) and HIV.

Consequently, correctional services and other related departments throughout southern Africa are facing mounting pressure to provide better health care for prisoners. In response to this pressure, nineteen heads of correctional services from all over Africa – meeting in Swaziland at an All African Symposium on Corrections in August 2007 – agreed to work together to address key challenges facing African prisons. Among other major challenges, they identified overcrowding, HIV/AIDS and inadequate medical care.

Why focus on prisoners when there are so many other marginalised groups who also struggle to access care?

First, prisoners – who lose their right to freedom of movement upon incarceration – still retain all their other basic human rights, including access to health care services. A South African appeal court decision that dates back almost 100 years laid down the fundamentals by accepting the residuum principle. This states that prisoners keep all their rights save for those that are necessary to impose the sentences of the courts.

Second, when the state deprives a person of his or her liberty, it assumes the responsibility to provide appropriate care. People deprived of their liberty cannot, when they are dissatisfied with the service received in a prison or police cell, go out and look for an alternative. They have no choice, being entirely dependent on the services provided to them by or on behalf of the state. It is this dependency that contributes to making them extremely vulnerable.

Third, 'good prison health is good public health'. Most prisoners are not incarcerated for life. Prisoners without effective TB and HIV programmes in detention facilities risk transmitting these diseases to people in their communities on release, further fuelling the TB and HIV pandemics. As a rule of thumb, the turnover of prisoners through the prison system is roughly three times the number in custody. In South Africa, for example, a correctional centre population of 162 000 means an annual turnover of 486 000 people moving through the system.

Finally, a large proportion of people in detention facilities have not yet been convicted of any crime. For example, 30% of South Africa's correctional centre inmates are still awaiting trial. Some of these prisoners may wait up to six years before their case is heard in court. Statistics on other countries are available on the International Centre for Prison Studies (ICPS) website.

2. BACKGROUND

Most prisoners in southern Africa are men between the ages of 18 and 45. In South Africa, 25 - 30% of prisoners are between 14 and 25 years old. A large proportion of these men come from poor communities with low educational standards and high rates of unemployment, homelessness and crime, all associated with increased risk of HIV. These factors may explain, at least in part, why the prevalence of HIV in prisoners is often appreciably higher than the rate in the general population. In Zomba prison in Malawi, for example, an HIV prevalence study revealed an astounding 74% of prisoners with HIV. Other sub-Saharan African countries have prison populations with an HIV prevalence of above 25%.

With already high HIV prevalence rates, issues related to imprisonment – including overcrowding, poor nutrition, disempowerment of the individual, dehumanising prison cultures, unprotected forced and consensual sex, stigmatisation, discrimination and poor access to health care – have a serious impact on rates of HIV infection, the rate of progression of HIV to AIDS and the incidence of opportunistic diseases. Some people enter the prison system with compromised health situations. This is reflected in the statistics showing that some 63% of all natural deaths in prisons occur within the first 36 months after admission to a detention facility. Simply put, incarceration itself may give rise to severe health consequences.

TB in particular has become a major problem in prisons. Overcrowding and poor ventilation contribute to vast numbers of prisoners contracting TB. For example, South Africa's correctional centres are currently running at 142% of capacity (over 160 000 prisoners were detained in 2007 in a system designed for just under 115 000). Within sub-Saharan African populations 70% of people with TB are HIV positive, and TB causes up to 40% of AIDS deaths. This interaction between HIV and TB is the most likely explanation for the massive increase in death rates occurring in southern African prisons. In South Africa, the number of correctional centre deaths rose by 584% between 1995 and 2000.

Access to ART has been shown to reduce the incidence of TB in people infected with HIV by up to 80%. Studies in both developed and developing countries have clearly shown that HIV treatment programmes are both feasible and effective in prisons. Such programmes should result in reduced prisoner morbidity and mortality, as well as lessening the number of new TB and HIV infections in the prison population and in their home communities.

Southern Africa is not alone in having to deal with the challenges raised by HIV/AIDS among prisoners. For an overview of the international perspective, see the United Nations Office on Drugs and Crime's *HIV/AIDS Prevention, Care, Treatment and Support in a Prison Setting: A Framework for an Effective Response* (2006) and the *Dublin Declaration on HIV/AIDS in Prisons in Europe and Central Asia:*

Prison Health is Public Health (2004), both of which are included in the bibliography at the end of this document.

3. DUTY OF THE HCW

HCWs are often put in difficult ethical positions in prisons, with dual and often conflicting loyalties to the authorities and to their patients. HCWs should be mindful of several cases that have defined international ethical guidelines and law, stretching from the infamous Steve Biko case involving doctors colluding in torture, to more recent episodes in Guantanamo Bay.

The Hippocratic Oath commits HCWs to work 'for the benefit of the sick according to [their] ability and judgment; keeping them from harm and injustice'. In addition, the World Medical Association's *Declaration of Tokyo – Guidelines for Physicians Concerning Torture and other Cruel, Inhuman or Degrading Treatment or Punishment in Relation to Detention and Imprisonment* expressly provides as follows:

'It is the privilege of the physician to practise medicine in the service of humanity, to preserve and restore bodily and mental health without distinction as to persons, to comfort and to ease the suffering of his or her patients. The utmost respect for human life is to be maintained even under threat, and no use made of any medical knowledge contrary to the laws of humanity. … A physician must have complete clinical independence in deciding upon the care of a person for whom he or she is medically responsible. The physician's fundamental role is to alleviate the distress of his or her fellow human beings, and no motive, whether personal, collective or political, shall prevail against this higher purpose.'

It is therefore the role of HCWs to act as advocates for access to health care, and not to restrict or ration care. The ethical duty of a HCW is to treat patients in a manner that serves their best interests, ensuring the 'right of everyone to the enjoyment of the highest attainable standard of physical and mental health' – as recognised in Article 12 of the *International Covenant on Economic, Social and Cultural Rights* – without discrimination.

This may mean that HCWs come into conflict with authorities while conducting their duties. Where necessary, HCWs may need to ask their representative associations – whether trade unions or professional bodies – for support when professional, ethical and/or legal guidance is needed. In addition, a range of legal and human rights organisations working in the field of HIV/AIDS could also be approached.

4. AIM OF THESE GUIDELINES

These guidelines are primarily aimed at promoting best practice for the prevention and treatment of HIV infection and related co-morbidities in detention facilities. In addition, they are intended to:

- Provide guidance to HCWs working with prisoners, whether within or outside a detention facility (e.g. a doctor providing care to a prisoner attending a public clinic), with a particular focus on their ethical and clinical responsibilities;
- Frame the expectations of prisoners and their families regarding appropriate levels of health care; and
- Guide governments, professional bodies and other organisations involved in the development and implementation of HIV-related policy in respect of prisoners. While this document is not official policy, it should nevertheless be considered as current good practice when policy is formulated.

5. SCOPE OF THESE GUIDELINES

These guidelines cover the provision of HIV-related health care to persons held in the following situations:

- Detention in police custody, with or without charge;
- Incarceration of prisoners awaiting trial, convicted and/or sentenced;
- Detention in military custody;
- Detention while awaiting deportation;
- Incarceration of children (persons below 18 years); and
- Infants and/or children accompanying persons in any of the above situations.

While the principles of care may be similar, these guidelines are not intended to provide guidance in respect of persons detained solely for medical reasons (e.g. persons detained for psychiatric care).

It is important to note that these guidelines do not provide comprehensive guidance for the prevention and treatment of HIV infection and related co-morbidities in detention facilities. They focus primarily on the particular challenges posed by such facilities and in working with prisoners with HIV. Unless specifically mentioned, the provision of health care should *at least be in accordance with standard adult and paediatric guidelines for the relevant country.* Because detention facilities vary widely, both within and between countries, HCWs should use their discretion and common sense when interpreting and applying these guidelines.

6. RESPONSIBILITIES AND RIGHTS OF THE HCW

As already mentioned, it is the role of HCWs to act, within a legal framework, as advocates for access to health care, and not to restrict or ration care.

- Practitioners should be constantly aware of the lack of volition of prisoners. They are a highly vulnerable population, unable to act independently. Access to care is often limited by non-medical staff (e.g. not allowing attendance at a clinic) and environmental circumstances (e.g. lack of transport or restrictions during lockdown). HCWs should intervene if limitations are compromising patient care.
- Furthermore, responsibilities may extend to other prisoners and detention facility staff. For instance, TB control may require interventions beyond individual patient care.
- Levels of medical and support staffing should meet the health needs of prisoners. Previously acceptable levels may no longer be adequate in the context of the HIV and TB pandemics. HCWs should advocate for adequate staffing.

HCWs have the right to a safe working environment. Detention facilities should therefore ensure:

- Good infection control, which includes:
  - adequate ventilation and exposure to sunlight (or ultraviolet germicidal irradiation where not practical); and
  - appropriate personal protective equipment; and
- Adequate protection from threats or acts of violence.

Rights of prisoners and their implications for HCWs:

- Prisoners retain the right to health care and the right to be treated with dignity. In addition to the rights recognised in the common law, domestic prison legislation and constitutions, a range of international human rights instruments address the rights of detained persons.
- Prisoners retain the right to refuse treatment. However, HCWs should be cognisant of the lack of information in prisons, and therefore their role as advocates for their patients' health carries greater weight than in the general population. HCWs should satisfy themselves in all situations that refusal of treatment is based on an informed decision, as is widely recognised as an integral part of informed consent laws.

7. CONFIDENTIALITY

Confidentiality of private medical information should be maintained, as is the case in respect of all patients. However, this may be difficult or even impossible in certain circumstances. Inadvertent disclosure to non-medical staff and other prisoners is common, especially where HIV-specific care is provided (e.g. an ART clinic within a prison). Provision of special diets, attendance on certain days and at certain clinics, calls for medication, legal consultations and storage of medication within cells may all lead to inadvertent disclosure.

Prisoners should be educated regarding disclosure and encouraged to disclose relevant medical information to allow the staff of the facility or the HCW to take the necessary steps to allow for appropriate medical care, such as the uninterrupted delivery of essential chronic medication. It is also necessary that security staff be trained to deal with sensitive and confidential medical information.

Personal safety of the HCW should not be placed at risk in the interests of protecting confidentiality. Guards may need to be present during consultations, and should hold in confidence all that is heard, as part of their professional duty. Provision should be made for the volunteering of confidential information out of earshot of guards, if necessary. Examinations should occur in a dignified fashion (e.g. behind a screen).

Written communication to other HCWs at distant sites should be sealed, to ensure that medical details are not available to guards and couriers. In detention facilities, prisoners sometimes provide health care support services and assist with administration. These prisoners should be trained to deal with sensitive and confidential medical information, to ensure that confidentiality is maintained at all times.

HCWs should be mindful of all of the above, and ensure confidentiality is not compromised unnecessarily.

8. PROVISION OF CARE FOR ALL PRISONERS

All prisoners, irrespective of HIV status, should have an immediate brief health assessment on entry to a detention facility to establish medical treatment status (see appendix for an example). Ordinarily, any immediately available member of staff who has been adequately trained can conduct this assessment. However, confidential information may be disclosed – the prisoner may have been assaulted prior to admission, and an affidavit from the person doing the assessment will be required. A security staff member will not be able to do this.

As part of the assessment, it is critical accurately to assess the following:

- Current medication requirements;
- Whether the prisoner has medication on his or her person;
- Where the prisoner previously obtained his or her care, and whether there are any medical records available; and
- Access to current and future medication needs.

If a prisoner is on any chronic treatment, all necessary steps should be taken to ensure that he or she is able to continue medication without interruption.

On admission to any site other than a short-term holding facility (where he or she is held for only a few days), timely access to the following services should be ensured for all prisoners:

- A comprehensive medical history and examination.
- HIV counselling and testing. This is to ensure timely access to appropriate health care, in particular TB prevention and early diagnosis. This must be clearly communicated to the prisoner, who may have concerns as to the motivation for testing. If HIV testing is refused, it must be actively pursued at future health visits.
- TB history, symptom screening and appropriate investigation.
- Sexually transmitted infection symptom screening and appropriate syndromic management.
- In the case of women, specific history in respect of pregnancy and fertility choices, and whether a cervical cytological screen (Pap smear) was ever performed.
- Children accompanying prisoners should also be assessed and immunisation status ascertained.
- Baseline clinical characteristics, including weight, blood pressure, urinalysis and nutritional assessment. Weight should be measured in a consistent manner, with shackles either in place (where permitted by law) or removed.
- If the prisoner is HIV positive, appropriate clinical and laboratory staging should be done according to national guidelines. However, note the recommendation below to initiate ART at a higher CD4 count, owing to the high risk of TB in people in a detention facility.

All prisoners (irrespective of HIV status) should have TB symptom screening and have their weights documented quarterly. This may be done by non-medical personnel, provided they have been appropriately trained. Prisoners who are unaware of their HIV status or who have tested negative previously, should be encouraged to be tested for HIV regularly.

9. CARE FOR HIV-INFECTED PATIENTS

Normal standards of care, except where noted below, should be according to national HIV management and treatment guidelines. This includes:

- Regular clinical and laboratory evaluations;
- Education and treatment literacy;
- Adherence support (e.g. support groups, alarm clocks);
- Appropriate and timely prophylaxis and treatment of opportunistic infections;
- ARV initiation and follow-up;
- Appropriate nutritional interventions; and
- Management of treatment complications.

In view of the dual pandemics of TB and HIV, and the clear benefit of ART in preventing TB, the initiation of ART in adults at a higher CD4 count (350 cells/µl) should be strongly considered.

Directly observed treatment (DOT) programmes for ART have yet to be shown to be effective in ensuring adherence in the prison setting. In our experience DOT approaches often result in missed doses owing to inadequate staffing, and are therefore not recommended. This could be reconsidered once better programmes have been designed and shown to be effective. Kept on person (KOP) programmes appear to have better outcomes.

Access to immediate care is often compromised in prisoner populations. Patients with HIV may require urgent interventions and experience substantial difficulties in accessing emergency care. A protocol to deal with these situations should be in place at each site. Guards should be trained to detect any visible deterioration or common signs or symptoms in HIV-infected patients.

Treatment that is required on an ongoing basis should be readily available. This includes access to TB treatment, isoniazid (INH), co-trimoxazole, fluconazole, and specific nutritional interventions.

HIV support is key to acceptance of HIV status as well as to continued adherence to ART. Disclosure has unique implications in detention facilities. Family members may not be readily available, and are often not aware of the prisoner's health status. Disclosure of HIV status to family members should be encouraged and assisted, noting that rejection may be particularly devastating in an already isolated person. Disclosure to an adherence supporter and access to support groups must be encouraged, but lack of disclosure should not be used as an exclusionary criterion for the provision of ART.

10. TB AND OTHER DISEASES OF INSTITUTIONALISATION

Prisoners with HIV are particularly vulnerable to certain illnesses associated with institutionalisation and overcrowding, such as TB, non-typhoidal salmonellosis, scabies, infectious enteric disease, invasive pneumococcal disease and herpes zoster virus (HZV). Prisoners are also more susceptible to the complications of influenza, hepatitis B and malaria. Appropriate vaccinations should be considered, including influenza, HZV and rotavirus. Pneumococcal vaccine should be provided for all HIV-infected children. Only adults established on ART, with CD4 counts above 200 cells/µl, should be given this vaccine.

Medical staff should react appropriately to reports of outbreaks, and notify authorities with the necessary urgency.

All people with suspected TB should be strongly encouraged to have an HIV test.

TB culture and drug susceptibility testing on all TB specimens should be standard of care for prisoners and staff, in view of the immediate consequences for the individual and other prisoners and staff in close proximity. TB sputum specimens must be collected in a well-ventilated and sunny area, preferably outside.

10.1 INH PROPHYLAXIS

INH prophylaxis is effective in preventing TB in HIV-infected people. After excluding active TB disease, all HIV-infected prisoners should receive continuous INH prophylaxis. Tuberculin skin testing is unnecessary. Although INH reduces the risk of TB significantly, TB must be entertained as a diagnosis in all patients on INH prophylaxis with suggestive symptoms and signs. INH should be continued until release from the detention facility. It is unclear whether there is benefit in providing INH prophylaxis in patients already on ART. The panel believes it should be used, unless evidence becomes available to the contrary, owing to the high risk of TB in detention facilities generally. ART and INH prophylaxis should not be initiated concurrently (a month apart is suggested, with ART being prioritised), owing to the difficulty of differentiating shared toxicities.

10.2 ART AND TB

All patients with drug-resistant TB should have ART irrespective of CD4 count.

If the prisoner qualifies for ART, it should be started 2 - 4 weeks after TB treatment initiation. Concomitant drug toxicity and immune reconstitution syndromes should be actively managed (see Southern African HIV Clinicians Society adult treatment guidelines).

10.3 TB AND INFECTION CONTROL

All sputum smear- or culture-positive TB patients must be transferred to a separate designated isolation area within the facility, with adequate ventilation, sunlight (or, if not available, ultraviolet germicidal light) and infection control and treatment facilities. If a patient is identified as multi-drug-resistant TB infected, they should be transferred urgently to a dedicated inpatient treatment site.

11. MENTAL ILLNESS AND SUBSTANCE ABUSE

Depression is under-recognised in both institutionalised and HIV-infected people. Depression has been identified as one of the major factors that impairs adherence, and must be actively screened for and managed. Similarly, other forms of mental illness are often not recognised or under-treated.

Substance abuse, including alcohol, marijuana, cocaine, crystal methamphetamine, mandrax and heroin, may negatively affect adherence and immunological progression of HIV disease. Substance use is often highly secretive in the prison environment, and a high index of suspicion should be maintained. Interventions that are appropriate to the kind of substance abuse should be freely available (e.g. methadone programmes, substance-specific support groups) to support prisoners with addiction problems.

Misuse of efavirenz, including smoking of the drug, has been reported. This has implications for adherence and viral resistance in both the intended recipient and ARV-naïve HIV-infected prisoners who abuse it.

Cigarette smoking is very common among prisoners, and is associated with a significant increase in risk of several respiratory illnesses, including TB. Smoking should be discouraged and environmental exposure minimised.

12. NUTRITION

Clinicians should encourage a healthy diet, ideally three regular meals, including adequate fresh fruit and vegetables, with adequate portions. Practically, a target weight should be maintained (see Southern African HIV Clinicians Society nutritional guidelines). Ill patients, including TB patients, and pregnant and lactating women should have their diets evaluated and customised appropriately. Clinicians should note that food is often used as currency, and this may be a reason for loss of weight. Dieticians should be consulted for specialised cases.

Many prisoners' nutritional needs may not be met by institutional diets. Low-dose vitamins and minerals (recommended daily allowance level) may be beneficial in this situation. Specific deficiencies should be corrected. Other supplements should be discouraged, as drug interactions and impact on the immune system are unknown.

Mealtimes may be a major barrier to adherence, especially with those ARVs that require administration with meals and fluids. The routine of the institution may make adherence very difficult, especially as mealtimes may vary, and counselling should be sensitive to these realities.

13. SPECIAL POPULATIONS

13.1 INFANTS AND CHILDREN ACCOMPANYING PRISONERS

All HIV-exposed infants and children should have appropriate HIV testing, as well as access to prophylaxis and treatment according to national guidelines. Mothers should be supported with feeding choices. Children in detention facilities, irrespective of HIV status, are exposed to high levels of TB. INH prophylaxis should be provided to all HIV-infected children, and considered for those who are HIV negative. TB must first be actively excluded.

Clinicians should maintain a high level of suspicion for active TB disease, investigate aggressively and manage appropriately. Infants and children have different nutritional needs to adults, particularly if HIV infected or unwell, and this may require dietary modification and/or nutritional supplements. Immunisation schedules must be adhered to.

Recent evidence strongly suggests that initiation of infants on ART immediately after diagnosis of HIV is beneficial. This is recommended, especially as infants are at high risk of TB exposure.

13.2 CHILD PRISONERS

Children are highly vulnerable to HIV infection and therefore need appropriate life skills and sex education. To decrease the risk of sexual exploitation, children must be segregated from adults at all times. Adult prisoners must never be used to supervise children. Consent for HIV testing should be obtained according to national guidelines, cognisant that legal guardians may not be easily accessible, or that guardianship may legally reside with the detention facility.

13.3 WOMEN IN DETENTION FACILITIES

Women should have adequate access to health care, including pregnancy care, services to prevent mother-to-child transmission of HIV (PMTCT), and regular Pap smears. In deciding on appropriate ART, HCWs should not assume that women prisoners with HIV do not want future pregnancies.

13.4 FOREIGN NATIONALS

Incarcerated foreign nationals should have access to HIV care in line with local guidelines applicable to the general population. These prisoners may be deported or voluntarily leave the country upon release (see Southern African HIV Clinicians Society guidelines on displaced persons).

14. PREVENTION OF HIV INFECTION IN DETENTION FACILITIES

In many southern African countries, HIV prevalence among prisoners exceeds 30%. Generally, the prevalence of HIV in prisons is much higher than in the population as a whole. Hence exposure to bodily fluids within a detention facility carries a significantly greater chance of exposure to HIV than in the community. This underscores the need for comprehensive HIV prevention programmes in detention facilities.

Exposure to HIV in a detention facility could result from:

- Sex, whether consensual or non-consensual;
- Tattooing;
- Sharing of needles, razors and hair clippers;
- Violence; and
- Pregnancy, labour and breastfeeding.

With the exception of South Africa, consensual sex between adult men is effectively criminalised in all southern African countries. While the criminalisation of consensual sex between women is less common, it exists in at least four southern African countries. Notwithstanding criminalisation, it is well recognised that consensual and non-consensual sexual activity takes place in detention facilities. HIV prevention programmes, including the need for access to PEP services, should acknowledge this reality.

HIV prevention programmes in detention facilities should at least include the following components:

14.1 EDUCATION

All prisoners should be offered and encouraged to participate in ongoing educational programmes that address HIV risk and management, including a focus on wellness and access to ART. In addition, these programmes should clearly identify and explain the range of HIV-related services available in the particular detention facility, as well as include clear messages regarding unsafe sex and other HIV exposure risks. Peer education programmes may be particularly effective in detention facilities. Appropriate programmes for peer educators should therefore also be provided.

14.2 HIV TESTING

In addition to providing a gateway to accessing appropriate treatment and care, HIV testing plays a crucial role in HIV prevention. It should therefore form an integral part of any HIV prevention programme. In particular, HIV testing services must be actively promoted and readily accessible, with access not being dependent on the presence of a doctor. Pre- and post-test counselling remains critical in all situations. HIV testing must be encouraged among family members who have been or may be exposed to HIV-positive prisoners.

14.3 CONDOMS AND WATER-BASED LUBRICANT

Consistent and correct use of condoms remains an essential pillar of any HIV prevention programme. Water-based lubricant is essential to minimise condom tearing and mucosal trauma during anal sex. Condoms and water-based lubricant should therefore be freely and widely available in all detention facilities. Adequately stocked condom and lubricant dispensers should be placed in numerous discreet and accessible locations throughout detention facilities.

14.4 REDUCING VULNERABILITY TO RAPE AND OTHER FORMS OF SEXUAL ASSAULT

With their consent, prisoners who are identified as extremely vulnerable to sexual assault may need to be separated from the general prison population upon admission. Once separated, they should be given a thorough orientation about prison life and the dangers of sexual assault and coercion. In addition to this specific intervention, authorities should develop and implement anti-rape strategies and consistently be aware of the need to minimise the risk of sexual assault.

14.5 PEP

PEP services should be freely available and accessible at all times, particularly because sexual assault is common in many detention facilities. Access to PEP should be guaranteed for all prisoners who could benefit from it and must not be dependent on the lodging of criminal charges and/or complaints. Provision of PEP services for those who have been exposed to bodily fluids through sex (whether consensual or non-consensual), trauma, workplace injury (including needle sticks) and needle sharing should be in accordance with local guidelines (or the Southern African HIV Clinicians Society Guidelines on PEP).

14.6 SUBSTANCE USE

Substance use – including the use of alcohol – is associated with a loss of inhibition and may lead to high-risk behaviour, particularly in detention facilities. Facility-specific harm reduction programmes should therefore be developed and implemented, taking into account local substance-use patterns.

There is clear evidence that needle exchange programmes for injecting drug users decrease HIV transmission. However, injecting drug use in southern African detention centres appears to be uncommon and the provision of potentially dangerous items directly to prisoners may not be feasible or indeed desirable. Nevertheless, officials are still advised seriously to consider needle exchange programmes where there is evidence of injecting drug use in any detention facility. In so doing, they should consider best practices adopted in detention facilities in other parts of the world, such as Moldova and other eastern European countries.

14.7 MALE CIRCUMCISION

Male circumcision is increasingly being recognised as an essential component of HIV prevention programmes. Male prisoners should not be prevented from accessing circumcision services, which should be provided in accordance with local policies. Where male prisoners access such services, they must be offered adequate counselling regarding risk reduction after circumcision.

14.8 SOAP AND DISINFECTANT

Soap and disinfectant should be made available and their use promoted in cleaning shaving blades, clippers and needles.

14.9 PREVENTION PROGRAMMES FOR HIV-POSITIVE PRISONERS

HIV prevention programmes tailored for those who have knowledge of their HIV-positive status appear to yield good results in terms of risk reduction behaviour. Each detention facility's prevention programme should expressly address those living with HIV, covering all the issues listed above.

15. CONTINUITY OF CARE

Continuity of care can be a challenge to both prisoner and HCW. Medication supply and communication between HCWs is often interrupted during the process of being incarcerated, movement between facilities and return to the community. There is a high risk of repeat incarceration in the prison population, which may further disrupt care.

As already indicated, all prisoners should have an immediate brief health assessment on admission to a detention facility. If the prisoner is using any chronic medication, all necessary steps should be taken to ensure that he or she is able to continue medication without interruption or resume treatment as soon as possible.

Awaiting-trial prisoners are particularly vulnerable, as they may be moved unexpectedly between courts, new incarceration areas, or even released. All such prisoners should be provided with a good medical summary using, where

necessary, official documentation, with clear instructions for further follow-up. Prisoners who are still on TB treatment should not be released without active planning for their continued treatment and written referral to their community TB clinic.

Transfer between institutions should be accompanied by a plan to ensure communication of all relevant medical information, as well as ensuring ongoing supply of medication at the new site. No transfer should take place unless ongoing treatment can be confirmed at the new site. The prisoner's medical file ideally should travel with the prisoner. Where this is not possible, the record should be sealed before being sent to the medical staff member at the receiving facility.

While the patient is incarcerated, appointments should not be compromised owing to lack of transport or other concerns. Escape concerns mean that scheduled visits are often not adhered to, and prisoners may miss off-site appointments. Uninterrupted medication should be arranged in these instances. Prisoners who access treatment off-site should have access to these services sooner should they require more urgent care.

Ideally, to minimise these situations adequate ART and other services should be provided on-site within the detention facility, and all adjuvant therapies, including the treatment of opportunistic infections and palliation, should be available. In situations where stavudine is being used, a lactate meter on site, with adequate training of facility staff, can be very useful to rapidly diagnose lactic acidosis syndromes and exclude shamming.

Preparation for release should include a good medical summary with clear instructions for continued care and medication access, as per the usual guidelines for transfer to any medical site. Inmates should be assessed and counselled on the complexity of and challenges related to the changes in adherence support and environment. Increased access to alcohol, other drugs, new sexual freedom, a breakdown of the strict institutional daily routine and poor access to new accommodation may lead to poor adherence and loss to follow-up.

Disclosure to family members and sexual partners may be very complex, and support should be provided. Where appropriate, prisoners should be advised regarding social assistance. Parole officers can play a vital role in ensuring continuity of care. Day parole programmes introduce challenges in the continuum of care where HIV-specific services are only offered during office hours, and prisoners may need to be counselled about the need to remain on site on clinic days.

Patients on clinical drug trials who are incarcerated should have continuity of care preserved, and there should be access to the trial medical staff. This may require direct explanation to prison authorities.

16. SPECIAL ISSUES

16.1 MEDICAL PAROLE

HIV *per se* should not be a reason for medical parole (where it exists). Prisoners with terminal disease due to HIV complications (e.g. advanced disseminated Kaposi's sarcoma, cryptococcal meningitis where ART is not available) should be considered for parole as per local guidelines for terminal diseases. Parole procedures may take time, and this must be factored into any application consideration and parole regulations.

16.2 ALTERNATIVE THERAPIES

Alternative therapies, including traditional medicines, homeopathy and others, are commonly accessed by prisoners. While this right must be respected, prisoners with HIV must be warned of possible side-effects, drug interactions and the risk of unknown consequences on their immune systems.

16.3 PRIVATE HEALTH CARE

In certain countries, prisoners may have access to private health care. Prisoners should be encouraged to select a single trusted health care provider for continuity of care. This should not preclude requests for second opinions.

16.4 RESEARCH AMONG PRISONERS

There is a lack of data on clinical and other requirements of care for HIV-infected prisoners. Bureaucratic impediments to research are commonly experienced. Guards may refuse access to prisoners by researchers despite adequate official permission. Research should be actively pursued in this vulnerable group, and this information disseminated to all relevant authorities and interest groups without interference by officials.

16.5 COMPULSORY HIV TESTING

In some countries, the law allows for compulsory testing, including for HIV, in certain situations. In South Africa, for example, a 2007 amendment to sexual offences legislation allows for the compulsory HIV testing of alleged sexual offenders in certain circumstances. Pre- and post-test counselling is particularly important and complex in this situation.

16.6 SEGREGATION OF HIV-POSITIVE PRISONERS

This is unnecessary and should be discouraged. Segregation for TB is covered above.

16.7 OVERSIGHT OF DETENTION FACILITIES

HIV-infected prisoners are particularly vulnerable to poor health care. Access to the media, external complaints bodies and legal service providers are often limited. All countries should have mechanisms for prisoners to report perceived poor treatment anonymously. Independent evaluation of service provision should be a regular feature of all HIV programmes in these institutions. Prisoner representative organisations should be consulted whenever policy is being developed and implemented.

Further guidance on this issue can be obtained from the 2006 *Optional Protocol to the Convention against Torture and other Cruel, Inhuman or Degrading Treatment or Punishment* (OPCAT), which establishes an international inspection system for detention facilities. OPCAT sets out the general monitoring duty of medical staff, and importantly, deals with their proactive duties.

16.8 STAFF ISSUES

While the focus of these guidelines is on inmates, a comprehensive staff programme should include infection control, screening, education, exposure prevention and access to TB and HIV treatment. Staff should be regularly screened for HIV and TB (as staff with HIV are at an increased risk of TB), and should be counselled appropriately.

BIBLIOGRAPHY

Badri M, Wilson D, Wood R. Effect of highly active antiretroviral therapy on incidence of tuberculosis in South Africa: a cohort study. *Lancet* 2002; 359: 2059-2064.

Bick JA. Infection control in jails and prisons. *Clin Infect Dis* 2007; 45(8): 1047-1055.

Department of Correctional Services (South Africa). Basic Information. http://www.dcs.gov.za/WebStatistics (last accessed 20 March 2008).

Dolan K, Kite B, Black E, Aceijas C. HIV in prison in low-income and middle-income countries. *Lancet Infect Dis* 2007; 7(1): 32-41.

Dublin Declaration on HIV/AIDS in Prisons in Europe and Central Asia: Prison Health is Public Health (23 February 2004). http://www.iprt.ie/iprt/1204 (last accessed 20 March 2008).

Goyer KC. HIV/AIDS in prison: Problems, policies and potential. http://www.iss.co.za/Pubs/Monographs/No79/Content.html (last accessed 20 March 2008).

Hippocratic Oath. http://www.pbs.org/wgbh/nova/doctors/oath_classical.html (last accessed 20 March 2008).

Jürgens R. From evidence to action on HIV/AIDS in prisons: A report from the XVI International AIDS Conference, Infectious Diseases in Corrections Report (2006), http://www.idcronline.org/archives/sept06/article.html (last accessed 20 March 2008).

Stanfield v Minister of Correctional Services 2004 (4) SA 43.

SABCnews.com. HIV one of toughest hurdles for African prisons.

http://www.sabcnews.com/africa/southern_africa/0,2172,153912,00.html (last accessed 20 March 2008).

United Nations General Assembly. International Covenant on Economic, Social and Cultural Rights (ICESCR). http://www.unhchr.ch/html/menu3/b/a_cescr.htm (last accessed 20 March 2008).

United Nations General Assembly. Principles of Medical Ethics relevant to the Role of Health Personnel, particularly Physicians, in the Protection of Prisoners and Detainees against Torture and Other Cruel, Inhuman or Degrading Treatment or Punishment (resolution 37/194, 18 December 1982). http://www2.ohchr.org/english/law/medicalethics.htm (last accessed 20 March 2008).

United Nations Office on Drugs and Crime (UNODC). World Health Organization (WHO) and Joint United Nations Program on HIV/AIDS (UNAIDS), HIV/AIDS Prevention, Care, Treatment and Support in a Prison Setting: A Framework for an Effective Response. 2006. http://data.unaids.org/pub/Report/2006/20060701_hiv-aids_prisons_en.pdf (last accessed 20 March 2008).

World Health Organization (WHO). Interim Policy on Collaborative TB/HIV Activities (2004). http://www.who.int/hiv/pub/tb/tbhiv/en/ (last accessed 20 March 2008).

Whittaker and Morant v Roos and Bateman 1912 AD 92.

Wilson D, Ford N, Ngammee V, Chua A, Kyaw MK. HIV prevention, care and treatment in two prisons in Thailand. PLoS Med 2007; 4(6): 204. http://www.pubmedcentral.nih.gov/articlerender.fcgi?tool=pubmed&pubmedid=17593894 (last accessed 20 March 2008).

World Medical Association. Declaration of Tokyo: Guidelines for Physicians Concerning Torture and other Cruel, Inhuman or Degrading Treatment or Punishment in Relation to Detention and Imprisonment (1975). http://www.wma.net/e/policy/c18.htm (last accessed 3 April 2008).

MYTHBUSTERS

■ Prisoners get a better deal in detention facilities than the general population.

While it may be true that prisoners receive regular meals while many in the general population have no such food security, overall prisoners have the same, if not poorer, access to health care, medication, choice of service provider, etc. as the general population.

■ HIV-infected prisoners got the virus in prison.

There has not been much research into the rate of HIV infection among new admissions to detention facilities. Statistics often reflect a higher prevalence of HIV than the general population, but this is probably accounted for by the bias of the population group within detention facilities, who may often have engaged in high-risk behaviour before arrest. The majority of HIV infections are probably acquired before admission; this can be deduced from the high numbers of awaiting-trial prisoners who have CD4 counts below 200, which suggests longstanding HIV infection.

■ There is no sex in prisons, and therefore no access to condoms is needed.

Many authorities deny this, but sexual intercourse, both consensual and non-consensual, does occur in prisons. Condoms are therefore essential as part of an HIV prevention programme in all facilities.

■ Prisoners should not get care because the general population can't get care.

Prisoners have the same rights to health care as the general population. As much effort should therefore be made to provide health care that is accessible to prisoners as to the general population. Evidence shows that limited access to health care in detention facilities is often as a result of the same barriers that limit access to health care for the general population. Such barriers need to be addressed for all.

■ Don't treat prisoners, as they are criminals and don't deserve it.

Again, prisoners still have the right to health care, despite the choices they have made. Emotive thinking does not change this.

■ Prisoners get preferential treatment at hospitals.

This perception often arises because of the need for prisoners to be guarded to prevent their escape while receiving medical care at hospitals. Prisoners often move straight to the front of the queue at busy clinics – this is not preferential treatment, but is done to limit the time they are outside the detention facilities. Similarly, admission may require a private ward, for the sake of providing adequate 24-hour security.

■ Prisoners don't want to test for HIV.

This is not the case. Statistics of HIV testing uptake are not widely known, but many facilities have waiting lists for testing. As in the general population, adequate counselling will almost always facilitate testing.

RESOURCES

Websites on denialism and the science of HIV/AIDS:
http://www.aidstruth.org/
http://aidsmyth.blogspot.com/
http://scienceblogs.com/aetiology/
http://www.physics.smu.edu/~pseudo/AIDS/
http://scienceblogs.com/denialism/2007/05/who_are_the_denialists_part_i_1.php

Websites of relevant civil society organisations:
AIDS Law Project: http://www.alp.org.za
AIDS and Rights Alliance for Southern Africa (ARASA): http://www.arasa.info
Civil Society Prison Reform Initiative: http://www.communitylawcentre.org.za/Civil-Society-Prison-Reform
International Centre for Prison Studies (ICPS): http://www.kcl.ac.uk/depsta/rel/icps/home.html
Rape Crisis: http://www.rapecrisis.org.za/
Treatment Action Campaign: http://www.tac.org.za

CASE STUDY 1

Paul (28) has been arrested and charged with housebreaking. He had previously been arrested for petty theft but released after six months when that case was withdrawn. Paul has consulted a traditional healer recently because of a chronic cough and obvious weight loss. The healer suggested he take a potion called *uBhejane* for a period of three months. Paul has started the course of treatment but has not experienced any improvement. He reports to the prison clinic with a fever and productive cough. The sister suspects TB and sends the sputum sample for acid-fast bacilli (AFB) staining while she initiates a course of antibiotics that seem to give relief. She does suggest that Paul undergoes a HIV test, as he is not aware of his status. Paul refuses an HIV test because he does not believe he is at risk of infection.

The result of the sputum test is received and AFB organisms are seen. The clinic sister informs Paul of the results and suggests a chest X-ray and starting with TB treatment. She also advises him again to take an HIV test. Paul refuses an X-ray but agrees to an HIV test, and after he has undergone the counselling, the rapid test comes up positive. Paul is visibly shocked with the result, but agrees to submit a sample for a confirmatory test which is also positive.

Paul refuses the offer of TB treatment and requests access to *uBhejane* instead. The sister decides to allow Paul to seek counsel from his peers but only for a period of one week. He returns to her clinic within a week and agrees to start TB treatment but does not want ART. He is very compliant with his DOTS and improves rapidly but refuses further testing or treatment for HIV. He is, however, receptive to advice on lifestyle changes, stops smoking and has more interest in his health and diet.

The sister decides to continue her appeal for Paul to consider further testing and possibly starting ART.

CASE STUDY 2

John approaches his prison doctor, saying that a condom tore during consensual anal sex the previous evening. He was the passive partner and is concerned that the other man may have HIV, as he had TB the previous year. The prison does not provide lubricant to prisoners, although it is suggested in a national prison policy document.

The doctor counsels John, saying that an HIV test is indicated and that PEP may be considered. After consulting with the central office, it becomes clear to the doctor that PEP after consensual sex is not advocated in national policy.

John is found to be HIV positive and is counselled, especially concerning the need for continued use of condoms. His CD4 count is normal and he is commenced on INH prophylaxis in keeping with national guidelines. The prison doctor raises the issue of adequate access to lubricant with the prison authorities, and, despite initial resistance, finally succeeds in having lubricant dispensed alongside the condom providers.

CASE STUDY 3

Maria is 28 weeks pregnant when she is sentenced to five years' imprisonment. Prior to her arrest she had tested HIV positive and she is concerned about her own health and the health of her unborn child and her seven-year-old son Thabo.

Thabo was staying with her partner, Sipho, who has never been tested for HIV, but is aware of Maria's HIV status.

She undergoes a medical examination and is found to be in good health with no symptoms suggestive of active TB. Her CD4 count is 550.

She goes into labour at 37 weeks and delivers a baby girl weighing 2 700 g before she can be transferred to the nearest hospital. She did not access any PMTCT services prior to delivering the baby.

She is taken to the local provincial hospital where she is examined and found to have no complications related to her pregnancy or labour. Her new baby, Sindisiwe, is examined and found to be in good health. Sindisiwe is given a dose of nevirapine and feeding options are discussed with Maria. At first she considers breastfeeding, but then decides that she is unlikely to be able to breastfeed exclusively in prison. She is given a six-week supply of formula milk, advised on how to prepare the bottles and given a follow-up date for six weeks.

In prison, she is pressurised by the female warders to breastfeed and feeds predominantly formula milk, but occasionally gives breastmilk. She takes her baby back to the local hospital at six weeks. Sindisiwe is found to be underweight, is started on co-trimoxasole prophylaxis and undergoes HIV-PCR testing. Four weeks later she is told that Sindisiwe's HIV-PCR is positive, a CD4 count is done and a referral letter given for the closest paediatric ART site.

A few months later she is released from prison and returns home. She realises she has missed her child's appointment date and that Sindisiwe has not received any of her routine immunisations.

Over the next few months Sindisiwe is started on ART and receives her EPI vaccines, Maria is admitted to hospital with lobar pneumonia and is then also started on ART, Thabo undergoes testing and is found to be HIV negative, and finally Sipho agrees to be tested and discovers he is also HIV positive.

APPENDIX. BRIEF ASSESSMENT FORM

This form is to be used in either of the following circumstances in order to limit the number of different forms

Initial Health Assessment

(to be completed within 24 hours of admission to facility, to maintain continuity of care)

Transfer Record

(to be completed and kept on person, including by all awaiting trial prisoners who may be released or transferred at short notice)

Name: _____ Med/Prisoner No: _____
Name of Facility: _____Date admitted:_____

Medical History:
Has the patient ever been treated for the following illnesses?

☐ Diabetes ☐ Epilepsy ☐ Asthma
☐ Hypertension ☐ STD's ☐ Other

Any other illnesses/operations _____
_____

Special Investigations _____

Tuberculosis History
Has the patient ever had TB? ☐ No ☐ Yes When?_____ Site_____
If Yes, how many times?_____ How long was treatment taken for?_____

HIV
Has the patient previously tested for HIV? ☐ Yes ☐ No
If yes, result_____ Date Tested_____CD4_____VL _____Date_____ WHO____
If not tested, or previously tested negative, **offer VCT.**

Any allergies?_____ Alcohol history?_____ Drug use?_____

Current problems
Screen for the following TB symptoms: ☐ Cough? ☐ Night sweats? ☐Wt loss?
If any of these symptoms are present, send sputum for TB culture.
Any other health problems? _____
_____
_____

Current Treatment
☐ TB treatment Date started_____ Current regimen_____ _____Wt_____
☐ ARV's Date started _____ Current regimen_____ CD4_____VL_____
Treatment will last until_____ Arrange more meds_____Y/N ☐
☐ Co-trimoxazol Any other –specify_____

Healthcare Worker Check List

☐ TB screen done. Date_____ ☐ Special investigations_____
☐ HIV status positive, or HIV test offered ☐ Date of HIV Test_____ Follow up visit_____
☐ Sputum sent (if needed) **Does this patient urgently need to see a doctor? ☐Y ☐ N**

Does this patient urgently need any chronic medication,esp ARV's or TB treatment?☐ Y☐ N
Follow up plan_____
_____
_____

Name of assessor: **Contact Details** **Date assessed:**

This form is to be used in either of the following circumstances in order to limit the number of different forms

Initial Health Assessment ✓

(to be completed within 24 hours of admission to facility, to maintain continuity of care)

Transfer Record

(to be completed and kept on person, including by all awaiting trial prisoners who may be released or transferred at short notice)

Name: FRANS NKOSI Med/Prisoner No: 01837387

Name of Facility: LEUKOP Date admitted: 1·4·2008

Medical History:

Has the patient ever been treated for the following illnesses?

☐ Diabetes ☐ Epilepsy ☐ Asthma

☒ Hypertension ☒ STD's ☐ Other

Any other illnesses/operations Hx of U/Discharge 2005

Special Investigations

Tuberculosis History

Has the patient ever had TB? ☒ No ☐ Yes When?_____ Site_____

If Yes, how many times?_____ How long was treatment taken for?_____

HIV

Has the patient previously tested for HIV? ☐ Yes ☒ No

If yes, result_____ Date Tested_____ CD4_____ VL_____ Date_____ WHO____

If not tested, or previously tested negative, **offer VCT.** (WILL THINK ABOUT IT)

Any allergies? NIL Alcohol history? SOCIAL Drug use? NIL

Current problems

Screen for the following TB symptoms: ☒ Cough? 3/52 ☒ Night sweats? ☐ Wt loss? NOT SURE

If any of these symptoms are present, send sputum for TB culture.

Any other health problems? SENDING SPUTUM FOR CULTURE
BLOOD PRESSURE - BP 130/80 - HAS Rx
NIL ELSE, WILL CONSIDER HIV TEST.

Current Treatment

☐ TB treatment Date started NO Current regimen_____ _____Wt_____

☐ ARV's Date started NO Current regimen_____ CD4_____ VL_____

Treatment will last until_____ Arrange more meds_____ Y/N☐

☐ Co-trimoxazol Any other –specify_____

Healthcare Worker Check List

☒ TB screen done. Date 1/4/2008 ☐ Special investigations SPUTUM SENT.

☐ HIV status positive, or HIV test offered ☐ Date of HIV Test_____ Follow up visit_____

☐ Sputum sent (if needed) **Does this patient urgently need to see a doctor?** ☒ **Y** ☐ **N**

Does this patient urgently need any chronic medication,esp ARV's or TB treatment? ☐ **Y** ☐ **N**

Follow up plan MAY REQUIRE TB TREATMENT.
ON HYPERTENSION MEDS - WILL REQUIRE 1/12ly.
HAS ENOUGH FOR 2/52.
CONCERN: COUGH + N/SWEATS - POSSIBLE CXR.

Name of assessor: Dr JONES **Contact Details** 011 488-3576 **Date assessed:** 1·4·08

This form is to be used in either of the following circumstances in order to limit the number of different forms

Initial Health Assessment

(to be completed within 24 hours of admission to facility, to maintain continuity of care)

Transfer Record ✓

(to be completed and kept on person, including by all awaiting trial prisoners who may be released or transferred at short notice)

Name: JACOB MAZIBUKO Med/Prisoner No: C183713 8

Name of Facility: MODER B Date admitted: 14·2·2001

Medical History:

Has the patient ever been treated for the following illnesses?

☐ Diabetes ☐ Epilepsy ☐ Asthma

☒ Hypertension ☐ STD's ☐ Other

Any other illnesses/operations GUNSHOT ABDOMEN JAN 2001.

Special Investigations

Tuberculosis History

Has the patient ever had TB? ☐ No ☒ Yes When? 2002 Site PULMONARY

If Yes, how many times? ×1 How long was treatment taken for? 6 MONTHS.

HIV

Has the patient previously tested for HIV? ☒ Yes ☐ No

If yes, result (+)VE Date Tested 3/10/02 CD4 180 VL 750 000 Date 11/11/02 WHO TM

If not tested, or previously tested negative, **offer VCT.**

Any allergies? NO Alcohol history? Yes Drug use? DAGGA

Current problems

Screen for the following TB symptoms: ☒ Cough? ☐ Night sweats? ☐ Wt loss?

If any of these symptoms are present, send sputum for TB culture.

Any other health problems? SPUTUM SENT OFF : CULTURE NEGMIVE DEC 2007.
CMV RETINITIS, INTRA-OCULAR GANCYCLOVIR @ JHB HOSPITAL - NEEDS REGULAR F/UP.

Current Treatment

☐ TB treatment Date started Current regimen Wt

☒ ARV's Date started 1/4/04 Current regimen 1a CD4 354 VL -40

Treatment will last until 30·4·2008 Arrange more meds YES Y/N ☒

☐ Co-trimoxazol Any other –specify GANCYCLOVIR @ JHB HOSPITAL ARLEN 256.

Healthcare Worker Check List

☒ TB screen done. Date FEB 2005, 12/2007 ☐ Special investigations

☐ HIV status positive, or HIV test offered ☐ Date of HIV Test Follow up visit

☐ Sputum sent (if needed) **Does this patient urgently need to see a doctor? ☒ Y ☐ N**

Does this patient urgently need any chronic medication,esp ARV's or TB treatment? ☐ Y ☐ N

Follow up plan 1) ARV CLINIC - JHB HOSPITAL NUMBER 47007082
2) OPTHALMOLOGY DEPT JHB HOSPITAL " "

Name of assessor: DR JONAS **Contact Details** 011 488-3556 **Date assessed:** 14·3·2008

GUIDELINES FOR RENAL REPLACEMENT THERAPY IN HIV-INFECTED INDIVIDUALS IN SOUTH AFRICA

South African Renal Society, South African Transplant Society, Southern African HIV Clinicians Society

1. DIALYSIS IN PATIENTS WITH HIV INFECTION

1.1 INTRODUCTION

HIV infection is common in southern Africa and presents our society with numerous challenges. HIV can cause chronic kidney disease (CKD) and can contribute significantly to the burden of patients requiring renal replacement therapy (RRT). HIV-associated nephropathy (HIVAN) was the third commonest cause of end-stage renal failure (ESRF) in black patients in the USA after hypertension and diabetes,[1] and since the availability of antiretroviral therapy (ART) is now in 7th place. Furthermore HIV infection may coexist with ESRF of any other cause, and we have even experienced instances of seroconversion to HIV positive of patients already on dialysis.

In southern Africa RRT is not freely available. Patients who can afford it or who have medical insurance may be able to receive these expensive therapies in the private sector in certain countries. The majority, however, do not have access to this service and it is provided to a select few in some state hospitals. Patients are selected for dialysis on the basis of state criteria for acceptance to a transplant programme (Appendix I).

In South Africa, even if patients with ESRF fulfil the state criteria most centres are limited by the availability of 'slots' for dialysis. These are defined by the institution on the basis of availability of funds, staff and equipment. Because the optimal form of RRT is renal transplantation, dialysis is seen as a bridge to transplant and the state 'criteria' are underpinned by the 'transplantability' of the patient. Any guideline on dialysis would have to keep this approach in mind, and the availability of dialysis for HIV-positive patients will be contingent on our ability to transplant them.

These guidelines are primarily aimed at South African clinicians, as limited dialysis and transplant facilities are available to them. There are none in most of the rest of southern Africa, but some countries have embarked on small-scale programmes, and can assess the relevance of the guidelines below to their situation.

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1.2 DIALYSIS IN HIV-POSITIVE PATIENTS

In the pre-HAART (highly active antiretroviral therapy) era the survival of most patients with advanced HIV infection was dismal. Similarly, for patients with HIV infection on dialysis the outcome was poor even in the developed world.[2] This led some practitioners to recommend withholding dialysis from these patients. After the advent of antiretrovirals (ARVs), however, several retrospective studies in Europe and the USA confirmed survival rates in the short term that were similar to the non-infected non-diabetic population.[3] Predictors of poor outcome include:[4]

- Low CD4 counts
- High viral loads
- HIVAN as the cause of ESRF
- Absence of HAART
- Opportunistic infections.

Given the finding that survival of HIV-positive patients receiving HAART is similar to that of non-infected dialysis pa-

SA Renal Society SA | Transplant Society | SA HIV Clinicians Society

tients, it has been recommended by guidelines in both the USA and the UK that dialysis not be withheld from these patients on the basis of their HIV serostatus.[5,6] However, the survival of HIV-positive patients on HAART on dialysis is still worse than that of the general HIV-positive population. Studies have shown a more rapid progression of HIV infection in patients with kidney failure, and evidence of kidney disease either in the form of proteinuria or a raised creatinine level portends a poorer outcome for the patient.[5] This has led to the initiation of transplantation in stable HIV-positive patients, with encouraging early results.

Both haemodialysis (HD) and peritoneal dialysis (PD) have been employed in HIV patients with ESRD. Review of the literature shows that both maintenance HD and PD are effective modes of RRT in these patients, although there are some points of concern with both modalities.[6,7]

1.2.1 Haemodialysis

Haemodialysis exposes the dialysis staff to blood products and contaminated needles. It is not necessary to haemodialyse patients in isolation units; the use of universal precautions is the best form of prevention of nosocomial infection.

Dialysis access in the form of an arteriovenous (AV) fistula is the best option for these patients, and similar patency rates to the non-infected population have been shown.[6,8] Some concern has been raised because of higher rates of polytetrafluoroethylene (PTFE) graft infection in HIV-positive patients, especially those with AIDS. This has led some to avoid permanent access if an AVF cannot be successfully created. However, the use of temporary catheters and permcaths for long-term use often leads to inadequate dialysis, not to mention the risks of infection, vascular occlusion and bleeding. HIV transmission in a dialysis unit has been documented via inadequate sterilisation of re-used needles.[9,10] Other infections have been caused by breaks in universal precautions and infection control procedures. Guidelines for infection control and machine disinfection set by the Association for the Advancement of Medical Instrumentation and the Centers for Disease Control should be adhered to at all times.

1.2.2 Peritoneal dialysis (CAPD)

Theoretically there is less exposure of staff to HIV-infected fluids with PD than with HD because peritoneal fluid is much less infectious than blood, there is less likelihood of a needle stick, and the nature of staff-to-patient contact is different. HIV was shown to survive in PD effluents at room temperature for up to 7 days and in PD exchange tubings for up to 48 hours. Both sodium hypochloride 50% (Amukin), and household bleach 10% solutions, in dilutions of 1:512, are effective in killing HIV in dialysate. Patients need to be educated on the need to dispose of these fluids properly. Peritoneal dialysis patients should be instructed to pour dialysate into the home toilet and to dispose of dialysate bags and lines by tying them in plastic bags and disposing of the plastic bags in conventional home garbage.[6,11]

CAPD may aggravate the malnutrition and hypoalbuminaemia in HIV patients with severe wasting syndrome. The rate of peritonitis was also higher in patients with low CD4 counts in the pre-HAART era. Both Gram-positive infections and *Pseudomonas* infection as well as fungal infections have been reported as being more common.[11]

Overall, given the fact that outcome does not seem to depend on modality of dialysis, the choice of RRT in HIV-infected patients should be based on an individual patient's lifestyle and preferences and availability of family and other support, and not on HIV seropositivity. In South Africa the dialysis modality offered will be further restricted by availability.

The substantial population prevalence of HIV infection (estimated at 6 million), even in a best-case scenario of a 1% prevalence of HIVAN in the infected population, would mean that 60 000 individuals would face this condition, which rapidly progresses to ESRF, without appropriate care. That comes to almost 1 200 patients per nephrologist! If only (conservatively again) 10% progressed to ESRF, this would mean an additional 6 000 individuals requiring dialysis – this is more than the current dialysis population in South Africa!

1.3 CHALLENGES AND RECOMMENDATIONS

1. Early detection of CKD and prevention of progression to ESRF is of prime importance. The importance of routine screening for kidney disease and appropriate early referral cannot be sufficiently stressed. Evidence indicates that treatment with HAART, angiotensin-converting enzyme (ACE) inhibitors and possibly steroids may slow or arrest progression to ESRF.[6] Early detection also allows for counselling and preparation of patients for RRT. This includes early initiation of HAART, exploring options for RRT, allowing patients to acquire a medical aid, preemptive transplantation and access creation.
2. Co-infection of these patients with hepatitis B and C may contribute to the burden of renal disease and also complicates therapy. Adequate diagnosis will allow for treatment.
3. Drug roll-out issues. To allow adequate access to dialysis, the availability of ARVs to patients with ESRF must be prioritised.
4. Opportunistic infections and malignancies in patients with extremely low CD4 counts may preclude transplantation. This is especially the case with certain infections such as cryptococcosis or malignancies such as Kaposi's sarcoma. (See HIV transplantation guidelines and Department of Health guidelines for other contraindications to renal transplantation.)
5. On the basis of current data we cannot justify excluding patients with HIV infection from receiving dialysis. Patients who are stable on HAART at the time of ESRF should not be treated any differently to other patients, whatever the cause of the ESRF. Similarly, patients in whom HIV infection is coincidental should be started on HAART as soon as possible and dialysis should not be withheld. Patients with advanced HIV disease who present acutely ill will need to be assessed on an indi-

vidual basis to determine whether dialysis will be offered. This will depend on the following considerations:

- Does the patient have acute reversible renal failure?
- What is the short-term prognosis of the patient?
- What is the availability of treatment at the centre?
- Would the patient be able to reconstitute his immune system? This may depend on several things including CD4 count, previous HAART, compliance and disease complications.
- Does the patient have a contraindication to renal transplantation, e.g. lymphoma?

2. GUIDELINES FOR MANAGEMENT OF KIDNEY TRANSPLANTATION IN HIV-INFECTED PATIENTS

2.1 INTRODUCTION

Before the introduction of HAART the morbidity and mortality of HIV-infected patients were considered to be too high to justify using scarce resources in transplanting infected patients. There were concerns that immunosuppression may accelerate HIV replication and result in rapid progression of the disease and increased mortality. Most reports on the effects of immunosuppressive agents (cyclosporine and mycophenalate mofetil) *in vitro*, on non-transplant HIV-infected patients and in HIV-infected transplant patients, have not shown detrimental effects and have in fact suggested that there may be beneficial effects.

2.2 MAIN RECOMMENDATIONS

All HIV-infected patients with CKD should be considered for RRT, including dialysis and transplantation.

Before listing for transplantation HIV-infected patients must demonstrate:

- Stability on HAART therapy with good adherence to treatment for at least 6 months.
- Absence of current AIDS-defining illness.
- CD4 count >200/µl for more than 6 months.
- Paediatric criteria:
  - <1 year of age – aim to get to 1 year or 10 kg before transplantation if possible
  - 1 - 6 years – CD4% >25% (but also consider absolute count)
  - >6 years – CD4 >200.
- Undetectable viral load (<50 copies/ml) for more than 6 months.

2.3 IMPORTANT CONSIDERATIONS

It has been well established that compliance with medication and clinic attendance is essential for successful management of both HIV infection and kidney transplantation. It is recommended that:

- Patients must be able and willing to attend close and regular follow-up.
- Patients must be willing to comply with antiviral and antifungal prophylaxis regimens.
- Patients must have a negative pregnancy test and be willing to use effective contraception for at least 2 years post-transplant.
- Women must have annual Pap smears before transplant, as well as mammograms.
- Adolescents will need extra support.
- Patients need to agree to be sent to a centre where a multidisciplinary approach including HIV specialists, nephrologists, dietitian and pharmacology support is available.

2.4 EXCLUSION CRITERIA

- Advanced cardiopulmonary disease
- Active uncontrolled malignancy with reduced life expectancy (see national guidelines for solid organ transplantation)
- Significant infection that may flare up or reactivate with immunosuppression (aspergillosis and other fungal infections, severe bacterial disease and active TB)
- Active human papillomavirus infection
- Evidence of liver cirrhosis (especially if co-infected with hepatitis B or hepatitis C virus)
- Untreated hepatitis B or hepatitis C co-infection with active viral replication – consider treatment for hepatitis B or hepatitis C first
- Documented progressive multifocal leukoencephalopathy
- Kaposi's sarcoma
- EBV and human herpesvirus 8 (HHV8)-associated lymphoproliferative diseases
- Active CMV
- Documented poor compliance.

2.5 HIV-RELATED CRITERIA FOR RENAL DIALYSIS AND TRANSPLANT PROGRAMMES

HIV infection should not be a reason for exclusion from renal dialysis or renal transplant programmes *per se*. However, like patients with other medical conditions the HIV-infected patient with ESRD needs to be assessed in terms of co-morbidities and psychosocial factors for suitability for these programmes.

Renal transplantation should only be undertaken in HIV-infected patients when the following criteria are met, in order to optimise the outcome after transplantation:

1. Patient on antiretroviral therapy (ART) for at least 6 months.
2. Adherence to ART is demonstrated and there is a commitment to lifelong therapy.
3. CD4 count >200 cells/µl.
4. HIV viral load undetectable.
5. No active opportunistic infections (OIs). If the patient has had a WHO stage 4 infection or TB they should have been fully treated and have been asymptomatic from this infection for at least 6 months.
6. No history of malignancies. However, if the patient has had a previous solid tumour that has been adequately treated and is now in remission they may be considered if they meet criteria for sufficient duration of remission prior to transplantation for HIV-uninfected patients (consult IPTTR prelisting).
7. Absence of certain HIV-related conditions:
   a. History of progressive multifocal leucoencephalopathy (PML)
   b. History of EBV or HHV-8-associated lymphoprolif-

erative disorders (lymphoma and multicentric Castleman's disease)
c. History of visceral Kaposi's sarcoma
d. Current advanced human papillomavirus-associated cervical or anal intra-epithelial neoplasia or carcinoma *in situ*.

Where resources are limited these are the most appropriate patients to consider for dialysis programmes as well. However, where resources permit, even HIV-infected patients who do not fulfil the CD4 and viral load criteria or have had recent OIs, but are committed to starting ART and maintaining adherence, may be considered for dialysis. The majority of such patients will subsequently fulfil these criteria when on ART (and when opportunistic infections have been treated).

In addition, in patients with the conditions described in 7b and 7c who are in remission transplantation with subsequent immunosuppressive therapy is inappropriate, but chronic dialysis should be offered for ESRD where possible. This also applies to patients with current advanced human papillomavirus-associated cervical or anal intra-epithelial neoplasia or carcinoma *in situ* (7d) in whom a transplant could be considered once these conditions have been optimally managed.

2.6 SOURCE OF ORGANS

Most units are using both cadaver and live related donors. Because most studies have shown nearly equivalent graft and patient survival with HIV-infected versus non-infected recipients, exclusion of HIV patients from the cadaver list cannot be justified.

Patients should be encouraged to use live related or unrelated donors wherever possible. It is generally considered essential that live donors are fully informed regarding the recipient's HIV status.

It is not currently considered safe to use HIV-infected donors, but little data are available.

2.7 IMMUNOSUPPRESSIVE PROTOCOLS

2.7.1. Induction

Most studies have shown that HIV-infected patients have at least as frequent and more acute rejection than non-HIV recipients. They should all be considered at 'high immunological risk'. It is considered safe to use monoclonal antibodies (basilixumab or dacluzimab), but polyclonal antibody induction therapy (OKT3) should be avoided. Some studies have had beneficial outcomes using thymoglobulin.

2.7.2. Maintenance protocols

It is generally believed that the apparent anti-HIV effects of cyclosporin and mycophenalate mofetil make these preferred first-line immunosuppression together with standard doses of prednisone.

Sirolimus, tacrolimus and azathioprine have been used, but there is very little literature available to support using them as first-line immunosuppression.

Because of interactions between immunosuppressive and antiretroviral drugs, regular drug level monitoring is essential. Once a stable immunosuppressive dose has been achieved the HAART therapy should only be changed under careful supervisison.

2.7.3. Acute rejection

A transplant renal biopsy should be considered in all cases of suspected rejection.

Standard high-dose/short-course corticosteroid therapy is considered optimal treatment for acute rejection.

2.8 TRANSPLANT KIDNEY BIOPSY

Many transplant units consider it essential to performprotocol biopsies, and units should inform potential recipients before the transplant that this policy may be adopted. Early biopsy may be indicated for delayed graft function or following an acute decline in renal function, but protocol biopsies should be considered at 1, 3 and 12 months.

2.9 PSYCHOLOGICAL ASSESSMENT AND SUPPORT

All potential recipients should have a full psychological assessment and identified problems should be managed appropriately. Following the transplant, the recipient, live donor and family may also need further support – this is especially true in adolescent patients.

2.10 HAART

Patients must be continued on full therapy following the transplant. It is essential that the transplant unit work with the HIV physician to ensure correct use of all drugs.

- Protease inhibitors (PIs) significantly affect metabolism of cyclosporine, tacrolimus and sirolimus, requiring dose reduction and increased time intervals.
- Efavirenz increases transplant drug requirements.
- Some drugs are antagonistic with mycophenolate and the combination may result in reduced antiviral effects. Stavudine is generally avoided, and zidovudine (AZT) must be used with care, as it shares toxicities with many transplant medications.
- Atazanavir is also usually avoided because of the frequent use of PPIs for acid suppression.

Several published guidelines exist describing interactions between drugs commonly used in HIV-positive recipients and immunosuppressants.

2.11 SPECIAL CONSIDERATIONS IN CHILDREN

- Adequate vaccination is important in children – especially live virus vaccines – prior to transplantation.
- INH prophylaxis is necessary in high-risk TB areas.

APPENDIX I: NATIONAL SOUTH AFRICAN HEALTH GUIDELINES FOR CHRONIC RENAL DIALYSIS

INTRODUCTION

It is the aim of the health services of South Africa to provide all South African citizens and permanent residents equita-

ble access to chronic renal dialysis. Dialysis is a method of removing waste products from the body for patients with kidney failure. The settings where dialysis is undertaken are: Hospitals, satellite units and homes.

These guidelines must therefore be used to make efficient use of limited resources and assist clinicians to decide who should be accepted onto the programme and who should not. Patients who do not satisfy these criteria but who are nevertheless accepted onto a chronic renal dialysis programme in the private sector, should remain the responsibility of the private sector. Kidney transplantation is the choice for many patients, but about a third are not suitable for transplantation and the supply of donor organs is limited.

However, owing to the lack of resources, it has to be accepted that there is a need to set boundaries for medical treatment, including renal dialysis.

OBJECTIVES

The main objectives of the guidelines are as follows:

- To optimise the use of scarce resources.
- To promote cost-effectiveness.
- To promote public/private partnership.
- To improve services to users.

1. PRINCIPLES

Unlike the public sector, renal transplantation should not be the major criterion for acceptance for chronic dialysis in the private sector.

Individual patients with diabetes and patients with acceptable co-morbid conditions may be considered for long-term renal dialysis, although research shows that they do not respond well in the long term.

Patients who satisfy the set criteria and are accepted onto a chronic dialysis programme in the private sector should remain the responsibility of the private sector provider unless there is timeous and specific agreement between the public and private sector to shift the responsibility.

Treatment options for chronic dialysis should be discussed with the patient and the family. They should be allowed to choose the technique that is optimal for the patient with due consideration of medical, social and geographical factors. Treatment that is offered should be cost-effective. In order to make an informed choice the potential impact on the patient's life and that of the family should be explained.

Physical and psychological symptoms related to chronic renal dialysis should be treated appropriately and monitored.

Public-private partnerships should be encouraged as a model for service delivery in chronic renal dialysis.

The service providers must take reasonable measures, within the resources available, to achieve the progressive realisation of the services to be offered.

2. EXCLUSION RATHER THAN INCLUSION CRITERIA SHOULD BE APPLIED FOR THE SELECTION OF A SUITABLE PATIENT

Before it is decided that dialysis is a suitable option for an individual, there should be a full assessment of the patient's health care needs such as economic, social, school and work circumstances. The consequences of long-term dialysis for the patient and their family are significant.

2.1 Medical exclusion criteria

- Active, uncontrollable malignancy or short life expectancy
- Advanced, irreversible progressive disease of vital organs such as:
  - cardiac, cerebrovascular or vascular disease
  - advanced cirrhosis and liver disease
  - medically or surgically irreversible coronary artery disease
  - lung disease
  - unresponsive infections e.g. HPV, hepatitis B and C.

2.2 HIV and AIDS are not medical exclusion criteria provided the patient has access to a comprehensive AIDS treatment plan including antiretroviral treatment and has been stable for at least 6 months and the above exclusion factors are absent.

2.3 Age (provided the above exclusion factors are absent) is not a contraindication to chronic renal dialysis. In the UK the median age of starting renal replacement therapy is 63 years and the median age of the population is 54 years.

2.4 Psychological exclusion criteria

- Any form of mental illness that has resulted in diminished capacity for patients to take responsibility for their actions.
- Active substance abuse or dependency including tobacco use.
- Obesity.

2.5 Compliance

Patients with proven habitual non-compliance with dialysis treatment and lifestyle modification will be excluded or removed from the chronic renal dialysis programme.

APPENDIX II: DIALYSIS REFERENCES

1. Ahuja TS, Collinge N, Grady J, Khan S. Is dialysis modality a factor in survival of patients with ESRD and HIV-associated nephropathy? *Am J Kidney Dis* 2003; 41(5): 1060-1064.
2. Feinfeld DA, Kaplan R, Dressler R, Lynn RI. Survival of human immunodeficiency virus-infected patients on maintenance dialysis. *Clin Nephrol* 1989; 32(5): 221-224.
3. Ahuja TS, Grady J, Khan S. Changing trends in the survival of dialysis patients with human immunodeficiency virus in the United States. *J Am Soc Nephrol* 2002; 13(7): 1889-1893.
4. Tourret J, Tostivint I, du Montcel ST, *et al.* I. Outcome and prognosis factors in HIV-infected hemodialysis patients. *Clin J Am Soc Nephrol* 2006; 1(6): 1241-1247.
5. Bhagani S, Sweny P, Brook G. Guidelines for kidney transplantation in patients with HIV disease. *HIV Med* 2006; 7(3): 133-139.
6. Gupta SK, Eustace JA, Winston JA, *et al.* Guidelines for the management of chronic kidney disease in HIV-infected patients: recommendations of the HIV Medicine Association of the Infectious Diseases Society of America. *Clin Infect Dis* 2005; 40(11): 1559-1585.
7. Soleymanian T, Raman S, Shannaq FN, *et al.* Survival and morbidity of HIV patients on hemodialysis and peritoneal dialysis: one center's experience and review of the

literature. *Int Urol Nephrol* 2006; 38(2): 331-338.
8. Ahuja TS, O'Brien WA. Special issues in the management of patients with ESRD and HIV infection. *Am J Kidney Dis* 2003; 41(2): 279-291.
9. Centers for Disease Control and Prevention. HIV transmission in a dialysis center – Colombia, 1991-1993. *JAMA* 1995; 274(5): 372-373.
10. Mandayam S, Ahuja TS. Dialyzing a patient with human immunodeficiency virus infection: what a nephrologist needs to know. *Am J Nephrol* 2004; 24(5): 511-521.
11. Rao TK. Human immunodeficiency virus infection in end-stage renal disease patients. *Semin Dial* 2003; 16(3): 233-344.

APPENDIX III: TRANSPLANT REFERENCES

1. Roland ME, Stock PG. Solid organ transplantation is a reality for patients with HIV infection. *Curr HIV/AIDS Rep* 2006; 3(3): 132-138.
2. Terrault NA, Carter JT, Carlson L, Roland ME, Stock PG. Outcome of patients with hepatitis B virus and human immunodeficiency virus infections referred for liver transplantation. *Liver Transpl* 2006; 12: 801-807.
3. Stock PG, Roland ME, Carlson L, *et al.* Kidney and liver transplantation in human immunodeficiency virus-infected patients: a pilot safety and efficacy study. *Transplantation* 2003; 76(2): 370-375.
4. Roland ME, Lo B, Braff J, Stock PG. Key clinical, ethical, and policy issues in the evaluation of the safety and effectiveness of solid organ transplantation in HIV-infected patients. *Arch Intern Med* 2003; 163(15): 1773-1778.
5. Roland ME, Carlson LL, Frassetto LA, Stock PG. Review of solid-organ transplantation in HIV-infected patients. *Transplantation* 2003; 75(4): 425-429.
6. Roland ME, Stock PG. Comprehensive guidelines translate research findings into clinical policy for HIV-infected transplant candidates and recipients. *Enferm Infecc Microbiol Clin* 2005; 23(6): 331-334.
7. Miró JM, Torre-Cisnero J, Moreno A, *et al.* GESIDA/GESITRA-SEIMC, PNS and ONT Consensus Document on Solid Organ Transplant (SOT) in HIV-Infected Patients in Spain (March, 2005). *Enferm Infecc Microbiol Clin* 2005; 23(6): 353-362.
8. Halpern SD, Ubel PA, Caplan AL. Solid-organ transplantation in HIV-infected patients. *N Engl J Med* 2002; 347(4): 284-287.
9. Kumar MS, Sierka DR, Damask AM, *et al.* Safety and success of kidney transplantation and concomitant immunosuppression in HIV-positive patients. *Kidney Int* 2005; 67(4): 1622-1629.
10. Abbott KC, Swanson SJ, Agodoa LY, Kimmel PL. Human immunodeficiency virus infection and kidney transplantation in the era of highly active antiretroviral therapy and modern immunosuppression. *J Am Soc Nephrol* 2004; 15(6): 1633-1639.
11. Neff GW, Bonham A, Tzakis AG, *et al.* Orthotopic liver transplantation in patients with human immunodeficiency virus and end-stage liver disease. *Liver Transpl* 2003; 9(3): 239-247.
12. Ragni MV, Belle SH, Im K, *et al.* Survival of human immunodeficiency virus-infected liver transplant recipients. *J Infect Dis* 2003; 188(10): 1412-1420.
13. Roland ME, Havlir DV. Responding to organ failure in HIV-infected patients. *N Engl J Med* 2003; 348(23): 2279-2281.
14. Roland ME, Adey D, Carlson LL, Terrault NA. Kidney and liver transplantation in HIV-infected patients: case presentations and review. *AIDS Patient Care STDS* 2003; 17(10): 501-507.
15. Samir K, Gupta JA, Eustace JA, *et al.* Guidelines for the Management of Chronic Kidney Disease in HIV-Infected Patients: Recommendations of the H1V Medicine Association of the Infectious Diseases Society of America. *Clin Infect Dis* 2005; 40(11): 1559-1585.
16. Roland ME, Barin B, Carlson L *et al.* HIV-infected liver and kidney transplant recipients: 1 and 3 year outcomes. *Am J Transplant* 2008; 8: 355-365.
17. Michelle E, Roland MD, Bernard L, *et al.* Key clinical, ethical, and policy issues in the evaluation of the safety and effectiveness of solid organ transplantation in HIV-infected patients. *Arch Intern Med* 2003; 163(15): 1773-1778.

APPENDIX IV. DOSAGE OF ANTIRETROVIRAL DRUGS FOR HIV-INFECTED ADULTS WITH CHRONIC KIDNEY DISEASE (CKD) OR RENAL DISEASE (ESRD) (TABLE 3, DIALYSIS REFERENCE 6, GUPTA SK, *et al.*)

Antiretroviral drug, dosing category	Dosage	Rating*	References
Nucleoside reverse transcriptase inhibitors			
Zidovudine†		B-II	[109-116]
Usual dosage	300 mg po bid		
Dosage for patients with CKD or ESRD			
Creatinine clearance ≥15 ml/min	No adjustment		
Creatinine clearance <15 ml/min	100 mg po q 6 - 8 h		
Receiving haemodialysis	100 mg po q 6 - 8 h‡		
Receiving peritoneal dialysis	100 mg po q 6 - 8 h		
Lamivudine†		B-I	[117-119]
Usual dosage	150 mg po bid/300 po qd		
Dosage for patients with CKD or ESRD			
Creatinine clearance ≥50 ml/min	No adjustment		
Creatinine clearance 30 - 49 ml/min	150 mg po qd		
Creatinine clearance 15 - 29 ml/min	150 mg po first dose, then 100 mg po qd		
Creatinine clearance 5 - 14 ml/min	150 mg po first dose, then 50 mg po qd		
Creatinine clearance <5 ml/min	50 mg po first dose, then 25 mg po qd		
Receiving haemodialysis	50 mg po first dose, then 25 mg po qd‡		
Receiving peritoneal dialysis	50 mg po first dose, then 25 mg po qd		
Abacavir§		B-I	[120]
Usual dosage	300 mg po bid/600 mg po qd		
Dosage for patients with CKD or ESRD			
All creatinine clearances	No adjustment		
Receiving haemodialysis	No adjustment‡		
Receiving peritoneal dialysis	Unknown, use with caution		
Stavudine immediate release (IR)		B-II	
Body weight ≥60 kg			
Usual dosage	30 mg po bid		
Dosage for patients with CKD or ESRD			
Creatinine clearance >50 ml /min	No adjustment		
Creatinine clearance 26 - 50 ml/min	20 mg po bid		
Creatinine clearance ≤25 ml/min	20 mg po qd		
Receiving haemodialysis	20 mg po qd‡		
Receiving peritoneal dialysis	Unknown, use with caution		
Body weight <60 kg			
Usual dosage	30 mg po bid		
Dosage for patients with CKD or ESRD			
Creatinine clearance >50 ml/min	No adjustment		

APPENDIX IV. CONTINUED

Antiretroviral drug, dosing category	Dosage	Rating*	References
Creatinine clearance 26 - 50 ml/min	20 mg po bid		
Creatinine clearance ≤25 ml/min	20 mg po qd		
Receiving haemodialysis	20 mg po qd†		
Receiving peritoneal dialysis	Unknown, use with caution		
Body weight <60 kg			
Usual dosage	30 mg po bid		
Dosage for patients with CKD or ESRD			
Creatinine clearance >50 ml/min	No adjustment		
Creatinine clearance 26 - 50 ml/min	15 mg po bid		
Creatinine clearance ≤25 ml/min	15 mg po bid		
Receiving haemodialysis	15 mg po qd†		
Receiving peritoneal dialysis	Unknown, use with caution		
Didanosine buffered tablets		B-II	[123, 124]
Body weight ≥60 kg			
Usual dosage	200 mg po bid		
Dosage for patients with CKD or ESRD			
Creatinine clearance ≥60 ml/min	No adjustment		
Creatinine clearance 30 - 59 ml/min	200 mg po qd		
Creatinine clearance 10 - 29 ml/min	150 mg po qd		
Creatinine clearance <10 ml/min	100 mg po qd		
Receiving haemodialysis	100 mg po qd†		
Receiving peritoneal dialysis	100 mg po qd		
Body weight <60 kg			
Usual dosage	125 mg po bid		
Dosage for patients with CKD or ESRD			
Creatinine clearance ≥60 ml/min	No adjustment		
Creatinine clearance 30 - 59 ml/min	150 mg po qd		
Creatinine clearance 10 - 29 ml/min	100 mg po qd		
Creatinine clearance <10 ml/min	75 mg po qd		
Receiving haemodialysis	75 mg po qd†		
Receiving peritoneal dialysis	75 mg po qd		
Didanosine EC			
Body weight ≥60 kg		B-II	[123-125]
Usual dosage	400 mg po qd		
Dosage for patients with CKD or ESRD			
Creatinine clearance ≥60 ml/min	No adjustment		
Creatinine clearance 30 - 59 ml/min	200 mg po qd		
Creatinine clearance 10 - 29 ml/min	125 mg po qd		
Creatinine clearance <10 ml/min	125 mg po qd		
Receiving haemodialysis	125 mg po qd†		
Receiving peritoneal dialysis	125 mg po qd		
Body weight <60 kg			
Usual dosage	250 mg po qd		
Dosage for patients with CKD or ESRD			
Creatinine clearance ≥60 ml/min	No adjustment		
Creatinine clearance 30 - 59 ml/min	125 mg po qd		
Creatinine clearance 10 - 29 ml/min	125 mg po qd		
Creatinine clearance <10 ml/min	Do not use; use buffered tablets instead		
Receiving haemodialysis	Do not use; use buffered tablets instead		
Receiving peritoneal dialysis	Do not use; use buffered tablets instead		
Emtricitabine		B-II	[127]
Usual dosage	200 mg po qd		
Dosage for patients with CKD or ESRD			
Creatinine clearance ≥50 ml/min	No adjustment		
Creatinine clearance 30 - 49 ml/min	200 mg po q 48 h		
Creatinine clearance 15 - 29 ml/min	200 mg po q 72 h		
Creatinine clearance <15 ml/min	200 mg po q 96 h		
Receiving haemodialysis	200 mg po q 96 h†		
Receiving peritoneal dialysis	Unknown, use with caution		

APPENDIX IV. CONTINUED

Antiretroviral drug, dosing category	Dosage	Rating*	References
Tenofovir		B-II	[128,129]
Usual dosage	300 mg po qd		
Dosage for patients with CKD or ESRD			
Creatinine clearance ≥50 ml/min	No adjustment		
Creatinine clearance 30 - 49 ml/min	300 mg po q 48 h		
Creatinine clearance 10 - 29 ml/min	300 mg po q 72 h		
Receiving haemodialysis	300 mg po every 7 days‡		
Receiving peritoneal dialysis	Unknown, use with caution		
Emtricitabine/tenofovir		C-III	[130]
Usual dosage	200 mg/300 mg po qd		
Dosage for patients with CKD or ESRD			
Creatinine clearance ≥50ml/min	No adjustment		
Creatinine clearance 30 - 49 ml/min	One tab po q 48 h		
Creatinine clearance <30 ml/min	Unknown, should not use combination tablet		
Non-nucleoside reverse transcriptase inhibitors			
Nevirapine		B-II	[131-135]
Usual dosage	200 mg po bid		
Dosage for patients with CKD or ESRD			
Creatinine clearance >20 ml/min	No adjustment		
Receiving haemodialysis	No adjustment‡		
Receiving peritoneal dialysis	Unknown, use with caution		
Efavirenz		C-III	[136-138]
Usual dosage	600 mg po qd		
Dosage for patients with CKD or ESRD	No adjustment		
Delavirdine		C-III	[139]
Usual dosage	400 mg po tid		
Dosage for patients with CKD or ESRD	No adjustment		
Protease inhibitors			
Indinavir		C-III	[140, 141]
Usual dosage	800 mg po tid		
Dosage for patients with CKD or ESRD	No adjustment		
Saquinavir soft gel		C-III	[132, 142, 143]
Usual dosage	1 200 mg po tid		
Dosage for patients with CKD or ESRD	No adjustment		
Saquinavir hard gel		C-II	[132, 142, 144]
Usual dosage	600 mg po tid		
Dosage for patients for CKD or ESRD	No adjustment		
Nelfinavir		C-III	[133, 145, 146]
Usual dosage	1 250 mg po bid		
Dosage for patients with CKD or ESRD	No adjustment		
Amprenavir		C-III	[147]
Usual dosage	1 200 mg po bid		
Dosage for patients with CKD or ESRD	No adjustment		
Fosampenavir		C-III	[148]
Usual dosage	1 400 mg po qd/700 mg po bid		
Dosage for patients with CKD or ESRD	No adjustment		
Ritonavir		C-III	[135, 142, 149]
Usual dosage	600 mg po bid		
Dosage for patients with CKD or ESRD	No adjustment		
Lopinavir/ritonavir		C-III	[150, 151]
Usual dosage	400 mg/100 mg po bid		
Dosage for patients with CKD or ESRD	No adjustment		
Atazanavir		C-III	[152]
Usual dosage	400 mg po qd		
Dosage for patients with CKD or ESRD	No adjustment		

APPENDIX IV. CONTINUED

Antiretroviral drug, dosing category	Dosage	Rating*	References
Entry/fusion inhibitors			
Enfuvirtide		B-II	[153]
Usual dosage	90 mg sc bid		
Dosage for patients with CKD or ESRD			
Creatinine clearance ≥35 ml/min	No adjustment		
Creatinine clearance <35 ml/min	Unknown, use with caution		

*The rating is for the recommendations on dose adjustment for patients with reduced renal function.

†Zidovudine/lamivudine (Combivir; GlaxoSmithKline) should be administered as separate component medications in patients with creatinine clearance <50 ml/min.

‡Administer either the daily dose or one of the daily doses after haemodialysis.

§Zidovudine/lamivudine/abacavir (Trizivir; GlaxoSmithKline) and lamivudine/abacavir (Epzicom; GlaxoSmithKline) should be administered as separate component medications in patients with creatinine clearance <50 ml/min.

GUIDELINES FOR RENAL REPLACEMENT THERAPY IN HIV-INFECTED INDIVIDUALS IN SOUTH AFRICA

South African Renal Society, South African Transplant Society, Southern African HIV Clinicians Society

1. DIALYSIS IN PATIENTS WITH HIV INFECTION

1.1 INTRODUCTION

HIV infection is common in southern Africa and presents our society with numerous challenges. HIV can cause chronic kidney disease (CKD) and can contribute significantly to the burden of patients requiring renal replacement therapy (RRT). HIV-associated nephropathy (HIVAN) was the third commonest cause of end-stage renal failure (ESRF) in black patients in the USA after hypertension and diabetes,[1] and since the availability of antiretroviral therapy (ART) is now in 7th place. Furthermore HIV infection may coexist with ESRF of any other cause, and we have even experienced instances of seroconversion to HIV positive of patients already on dialysis.

In southern Africa RRT is not freely available. Patients who can afford it or who have medical insurance may be able to receive these expensive therapies in the private sector in certain countries. The majority, however, do not have access to this service and it is provided to a select few in some state hospitals. Patients are selected for dialysis on the basis of state criteria for acceptance to a transplant programme (Appendix I).

In South Africa, even if patients with ESRF fulfil the state criteria most centres are limited by the availability of 'slots' for dialysis. These are defined by the institution on the basis of availability of funds, staff and equipment. Because the optimal form of RRT is renal transplantation, dialysis is seen as a bridge to transplant and the state 'criteria' are underpinned by the 'transplantability' of the patient. Any guideline on dialysis would have to keep this approach in mind, and the availability of dialysis for HIV-positive patients will be contingent on our ability to transplant them.

These guidelines are primarily aimed at South African clinicians, as limited dialysis and transplant facilities are available to them. There are none in most of the rest of southern Africa, but some countries have embarked on small-scale programmes, and can assess the relevance of the guidelines below to their situation.

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1.2 DIALYSIS IN HIV-POSITIVE PATIENTS

In the pre-HAART (highly active antiretroviral therapy) era the survival of most patients with advanced HIV infection was dismal. Similarly, for patients with HIV infection on dialysis the outcome was poor even in the developed world.[2] This led some practitioners to recommend withholding dialysis from these patients. After the advent of antiretrovirals (ARVs), however, several retrospective studies in Europe and the USA confirmed survival rates in the short term that were similar to the non-infected non-diabetic population.[3] Predictors of poor outcome include:[4]

- Low CD4 counts
- High viral loads
- HIVAN as the cause of ESRF
- Absence of HAART
- Opportunistic infections.

Given the finding that survival of HIV-positive patients receiving HAART is similar to that of non-infected dialysis pa-

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tients, it has been recommended by guidelines in both the USA and the UK that dialysis not be withheld from these patients on the basis of their HIV serostatus.[5,6] However, the survival of HIV-positive patients on HAART on dialysis is still worse than that of the general HIV-positive population. Studies have shown a more rapid progression of HIV infection in patients with kidney failure, and evidence of kidney disease either in the form of proteinuria or a raised creatinine level portends a poorer outcome for the patient.[5] This has led to the initiation of transplantation in stable HIV-positive patients, with encouraging early results.

Both haemodialysis (HD) and peritoneal dialysis (PD) have been employed in HIV patients with ESRD. Review of the literature shows that both maintenance HD and PD are effective modes of RRT in these patients, although there are some points of concern with both modalities.[6,7]

1.2.1 Haemodialysis

Haemodialysis exposes the dialysis staff to blood products and contaminated needles. It is not necessary to haemodialyse patients in isolation units; the use of universal precautions is the best form of prevention of nosocomial infection.

Dialysis access in the form of an arteriovenous (AV) fistula is the best option for these patients, and similar patency rates to the non-infected population have been shown.[6,8] Some concern has been raised because of higher rates of polytetrafluoroethylene (PTFE) graft infection in HIV-positive patients, especially those with AIDS. This has led some to avoid permanent access if an AVF cannot be successfully created. However, the use of temporary catheters and permcaths for long-term use often leads to inadequate dialysis, not to mention the risks of infection, vascular occlusion and bleeding. HIV transmission in a dialysis unit has been documented via inadequate sterilisation of re-used needles.[9,10] Other infections have been caused by breaks in universal precautions and infection control procedures. Guidelines for infection control and machine disinfection set by the Association for the Advancement of Medical Instrumentation and the Centers for Disease Control should be adhered to at all times.

1.2.2 Peritoneal dialysis (CAPD)

Theoretically there is less exposure of staff to HIV-infected fluids with PD than with HD because peritoneal fluid is much less infectious than blood, there is less likelihood of a needle stick, and the nature of staff-to-patient contact is different. HIV was shown to survive in PD effluents at room temperature for up to 7 days and in PD exchange tubings for up to 48 hours. Both sodium hypochloride 50% (Amukin), and household bleach 10% solutions, in dilutions of 1:512, are effective in killing HIV in dialysate. Patients need to be educated on the need to dispose of these fluids properly. Peritoneal dialysis patients should be instructed to pour dialysate into the home toilet and to dispose of dialysate bags and lines by tying them in plastic bags and disposing of the plastic bags in conventional home garbage.[6,11]

CAPD may aggravate the malnutrition and hypoalbuminaemia in HIV patients with severe wasting syndrome. The rate of peritonitis was also higher in patients with low CD4 counts in the pre-HAART era. Both Gram-positive infections and *Pseudomonas* infection as well as fungal infections have been reported as being more common.[11]

Overall, given the fact that outcome does not seem to depend on modality of dialysis, the choice of RRT in HIV-infected patients should be based on an individual patient's lifestyle and preferences and availability of family and other support, and not on HIV seropositivity. In South Africa the dialysis modality offered will be further restricted by availability.

The substantial population prevalence of HIV infection (estimated at 6 million), even in a best-case scenario of a 1% prevalence of HIVAN in the infected population, would mean that 60 000 individuals would face this condition, which rapidly progresses to ESRF, without appropriate care. That comes to almost 1 200 patients per nephrologist! If only (conservatively again) 10% progressed to ESRF, this would mean an additional 6 000 individuals requiring dialysis – this is more than the current dialysis population in South Africa!

1.3 CHALLENGES AND RECOMMENDATIONS

1. Early detection of CKD and prevention of progression to ESRF is of prime importance. The importance of routine screening for kidney disease and appropriate early referral cannot be sufficiently stressed. Evidence indicates that treatment with HAART, angiotensin-converting enzyme (ACE) inhibitors and possibly steroids may slow or arrest progression to ESRF.[6] Early detection also allows for counselling and preparation of patients for RRT. This includes early initiation of HAART, exploring options for RRT, allowing patients to acquire a medical aid, preemptive transplantation and access creation.
2. Co-infection of these patients with hepatitis B and C may contribute to the burden of renal disease and also complicates therapy. Adequate diagnosis will allow for treatment.
3. Drug roll-out issues. To allow adequate access to dialysis, the availability of ARVs to patients with ESRF must be prioritised.
4. Opportunistic infections and malignancies in patients with extremely low CD4 counts may preclude transplantation. This is especially the case with certain infections such as cryptococcosis or malignancies such as Kaposi's sarcoma. (See HIV transplantation guidelines and Department of Health guidelines for other contraindications to renal transplantation.)
5. On the basis of current data we cannot justify excluding patients with HIV infection from receiving dialysis. Patients who are stable on HAART at the time of ESRF should not be treated any differently to other patients, whatever the cause of the ESRF. Similarly, patients in whom HIV infection is coincidental should be started on HAART as soon as possible and dialysis should not be withheld. Patients with advanced HIV disease who present acutely ill will need to be assessed on an indi-

vidual basis to determine whether dialysis will be offered. This will depend on the following considerations:

- Does the patient have acute reversible renal failure?
- What is the short-term prognosis of the patient?
- What is the availability of treatment at the centre?
- Would the patient be able to reconstitute his immune system? This may depend on several things including CD4 count, previous HAART, compliance and disease complications.
- Does the patient have a contraindication to renal transplantation, e.g. lymphoma?

2. GUIDELINES FOR MANAGEMENT OF KIDNEY TRANSPLANTATION IN HIV-INFECTED PATIENTS

2.1 INTRODUCTION

Before the introduction of HAART the morbidity and mortality of HIV-infected patients were considered to be too high to justify using scarce resources in transplanting infected patients. There were concerns that immunosuppression may accelerate HIV replication and result in rapid progression of the disease and increased mortality. Most reports on the effects of immunosuppressive agents (cyclosporine and mycophenalate mofetil) *in vitro*, on non-transplant HIV-infected patients and in HIV-infected transplant patients, have not shown detrimental effects and have in fact suggested that there may be beneficial effects.

2.2 MAIN RECOMMENDATIONS

All HIV-infected patients with CKD should be considered for RRT, including dialysis and transplantation.

Before listing for transplantation HIV-infected patients must demonstrate:

- Stability on HAART therapy with good adherence to treatment for at least 6 months.
- Absence of current AIDS-defining illness.
- CD4 count >200/µl for more than 6 months.
- Paediatric criteria:
  - <1 year of age – aim to get to 1 year or 10 kg before transplantation if possible
  - 1 - 6 years – CD4% >25% (but also consider absolute count)
  - >6 years – CD4 >200.
- Undetectable viral load (<50 copies/ml) for more than 6 months.

2.3 IMPORTANT CONSIDERATIONS

It has been well established that compliance with medication and clinic attendance is essential for successful management of both HIV infection and kidney transplantation. It is recommended that:

- Patients must be able and willing to attend close and regular follow-up.
- Patients must be willing to comply with antiviral and antifungal prophylaxis regimens.
- Patients must have a negative pregnancy test and be willing to use effective contraception for at least 2 years post-transplant.
- Women must have annual Pap smears before transplant, as well as mammograms.
- Adolescents will need extra support.
- Patients need to agree to be sent to a centre where a multidisciplinary approach including HIV specialists, nephrologists, dietitian and pharmacology support is available.

2.4 EXCLUSION CRITERIA

- Advanced cardiopulmonary disease
- Active uncontrolled malignancy with reduced life expectancy (see national guidelines for solid organ transplantation)
- Significant infection that may flare up or reactivate with immunosuppression (aspergillosis and other fungal infections, severe bacterial disease and active TB)
- Active human papillomavirus infection
- Evidence of liver cirrhosis (especially if co-infected with hepatitis B or hepatitis C virus)
- Untreated hepatitis B or hepatitis C co-infection with active viral replication – consider treatment for hepatitis B or hepatitis C first
- Documented progressive multifocal leukoencephalopathy
- Kaposi's sarcoma
- EBV and human herpesvirus 8 (HHV8)-associated lymphoproliferative diseases
- Active CMV
- Documented poor compliance.

2.5 HIV-RELATED CRITERIA FOR RENAL DIALYSIS AND TRANSPLANT PROGRAMMES

HIV infection should not be a reason for exclusion from renal dialysis or renal transplant programmes *per se*. However, like patients with other medical conditions the HIV-infected patient with ESRD needs to be assessed in terms of co-morbidities and psychosocial factors for suitability for these programmes.

Renal transplantation should only be undertaken in HIV-infected patients when the following criteria are met, in order to optimise the outcome after transplantation:

1. Patient on antiretroviral therapy (ART) for at least 6 months.
2. Adherence to ART is demonstrated and there is a commitment to lifelong therapy.
3. CD4 count >200 cells/µl.
4. HIV viral load undetectable.
5. No active opportunistic infections (OIs). If the patient has had a WHO stage 4 infection or TB they should have been fully treated and have been asymptomatic from this infection for at least 6 months.
6. No history of malignancies. However, if the patient has had a previous solid tumour that has been adequately treated and is now in remission they may be considered if they meet criteria for sufficient duration of remission prior to transplantation for HIV-uninfected patients (consult IPTTR prelisting).
7. Absence of certain HIV-related conditions:
   a. History of progressive multifocal leucoencephalopathy (PML)
   b. History of EBV or HHV-8-associated lymphoprolif-

erative disorders (lymphoma and multicentric Castleman's disease)
c. History of visceral Kaposi's sarcoma
d. Current advanced human papillomavirus-associated cervical or anal intra-epithelial neoplasia or carcinoma *in situ*.

Where resources are limited these are the most appropriate patients to consider for dialysis programmes as well. However, where resources permit, even HIV-infected patients who do not fulfil the CD4 and viral load criteria or have had recent OIs, but are committed to starting ART and maintaining adherence, may be considered for dialysis. The majority of such patients will subsequently fulfil these criteria when on ART (and when opportunistic infections have been treated).

In addition, in patients with the conditions described in 7b and 7c who are in remission transplantation with subsequent immunosuppressive therapy is inappropriate, but chronic dialysis should be offered for ESRD where possible. This also applies to patients with current advanced human papillomavirus-associated cervical or anal intra-epithelial neoplasia or carcinoma *in situ* (7d) in whom a transplant could be considered once these conditions have been optimally managed.

2.6 SOURCE OF ORGANS

Most units are using both cadaver and live related donors. Because most studies have shown nearly equivalent graft and patient survival with HIV-infected versus non-infected recipients, exclusion of HIV patients from the cadaver list cannot be justified.

Patients should be encouraged to use live related or unrelated donors wherever possible. It is generally considered essential that live donors are fully informed regarding the recipient's HIV status.

It is not currently considered safe to use HIV-infected donors, but little data are available.

2.7 IMMUNOSUPPRESSIVE PROTOCOLS

2.7.1. Induction

Most studies have shown that HIV-infected patients have at least as frequent and more acute rejection than non-HIV recipients. They should all be considered at 'high immunological risk'. It is considered safe to use monoclonal antibodies (basilixumab or dacluzimab), but polyclonal antibody induction therapy (OKT3) should be avoided. Some studies have had beneficial outcomes using thymoglobulin.

2.7.2. Maintenance protocols

It is generally believed that the apparent anti-HIV effects of cyclosporin and mycophenalate mofetil make these preferred first-line immunosuppression together with standard doses of prednisone.

Sirolimus, tacrolimus and azathioprine have been used, but there is very little literature available to support using them as first-line immunosuppression.

Because of interactions between immunosuppressive and antiretroviral drugs, regular drug level monitoring is essential. Once a stable immunosuppressive dose has been achieved the HAART therapy should only be changed under careful supervisison.

2.7.3. Acute rejection

A transplant renal biopsy should be considered in all cases of suspected rejection.

Standard high-dose/short-course corticosteroid therapy is considered optimal treatment for acute rejection.

2.8 TRANSPLANT KIDNEY BIOPSY

Many transplant units consider it essential to performprotocol biopsies, and units should inform potential recipients before the transplant that this policy may be adopted. Early biopsy may be indicated for delayed graft function or following an acute decline in renal function, but protocol biopsies should be considered at 1, 3 and 12 months.

2.9 PSYCHOLOGICAL ASSESSMENT AND SUPPORT

All potential recipients should have a full psychological assessment and identified problems should be managed appropriately. Following the transplant, the recipient, live donor and family may also need further support – this is especially true in adolescent patients.

2.10 HAART

Patients must be continued on full therapy following the transplant. It is essential that the transplant unit work with the HIV physician to ensure correct use of all drugs.

- Protease inhibitors (PIs) significantly affect metabolism of cyclosporine, tacrolimus and sirolimus, requiring dose reduction and increased time intervals.
- Efavirenz increases transplant drug requirements.
- Some drugs are antagonistic with mycophenolate and the combination may result in reduced antiviral effects. Stavudine is generally avoided, and zidovudine (AZT) must be used with care, as it shares toxicities with many transplant medications.
- Atazanavir is also usually avoided because of the frequent use of PPIs for acid suppression.

Several published guidelines exist describing interactions between drugs commonly used in HIV-positive recipients and immunosuppressants.

2.11 SPECIAL CONSIDERATIONS IN CHILDREN

- Adequate vaccination is important in children – especially live virus vaccines – prior to transplantation.
- INH prophylaxis is necessary in high-risk TB areas.

APPENDIX I: NATIONAL SOUTH AFRICAN HEALTH GUIDELINES FOR CHRONIC RENAL DIALYSIS

INTRODUCTION

It is the aim of the health services of South Africa to provide all South African citizens and permanent residents equita-

ble access to chronic renal dialysis. Dialysis is a method of removing waste products from the body for patients with kidney failure. The settings where dialysis is undertaken are: Hospitals, satellite units and homes.

These guidelines must therefore be used to make efficient use of limited resources and assist clinicians to decide who should be accepted onto the programme and who should not. Patients who do not satisfy these criteria but who are nevertheless accepted onto a chronic renal dialysis programme in the private sector, should remain the responsibility of the private sector. Kidney transplantation is the choice for many patients, but about a third are not suitable for transplantation and the supply of donor organs is limited.

However, owing to the lack of resources, it has to be accepted that there is a need to set boundaries for medical treatment, including renal dialysis.

OBJECTIVES

The main objectives of the guidelines are as follows:

- To optimise the use of scarce resources.
- To promote cost-effectiveness.
- To promote public/private partnership.
- To improve services to users.

1. PRINCIPLES

Unlike the public sector, renal transplantation should not be the major criterion for acceptance for chronic dialysis in the private sector.

Individual patients with diabetes and patients with acceptable co-morbid conditions may be considered for long-term renal dialysis, although research shows that they do not respond well in the long term.

Patients who satisfy the set criteria and are accepted onto a chronic dialysis programme in the private sector should remain the responsibility of the private sector provider unless there is timeous and specific agreement between the public and private sector to shift the responsibility.

Treatment options for chronic dialysis should be discussed with the patient and the family. They should be allowed to choose the technique that is optimal for the patient with due consideration of medical, social and geographical factors. Treatment that is offered should be cost-effective. In order to make an informed choice the potential impact on the patient's life and that of the family should be explained.

Physical and psychological symptoms related to chronic renal dialysis should be treated appropriately and monitored.

Public-private partnerships should be encouraged as a model for service delivery in chronic renal dialysis.

The service providers must take reasonable measures, within the resources available, to achieve the progressive realisation of the services to be offered.

2. EXCLUSION RATHER THAN INCLUSION CRITERIA SHOULD BE APPLIED FOR THE SELECTION OF A SUITABLE PATIENT

Before it is decided that dialysis is a suitable option for an individual, there should be a full assessment of the patient's health care needs such as economic, social, school and work circumstances. The consequences of long-term dialysis for the patient and their family are significant.

2.1 Medical exclusion criteria

- Active, uncontrollable malignancy or short life expectancy
- Advanced, irreversible progressive disease of vital organs such as:
  - cardiac, cerebrovascular or vascular disease
  - advanced cirrhosis and liver disease
  - medically or surgically irreversible coronary artery disease
  - lung disease
  - unresponsive infections e.g. HPV, hepatitis B and C.

2.2 HIV and AIDS are not medical exclusion criteria provided the patient has access to a comprehensive AIDS treatment plan including antiretroviral treatment and has been stable for at least 6 months and the above exclusion factors are absent.

2.3 Age (provided the above exclusion factors are absent) is not a contraindication to chronic renal dialysis. In the UK the median age of starting renal replacement therapy is 63 years and the median age of the population is 54 years.

2.4 Psychological exclusion criteria

- Any form of mental illness that has resulted in diminished capacity for patients to take responsibility for their actions.
- Active substance abuse or dependency including tobacco use.
- Obesity.

2.5 Compliance

Patients with proven habitual non-compliance with dialysis treatment and lifestyle modification will be excluded or removed from the chronic renal dialysis programme.

APPENDIX II: DIALYSIS REFERENCES

1. Ahuja TS, Collinge N, Grady J, Khan S. Is dialysis modality a factor in survival of patients with ESRD and HIV-associated nephropathy? *Am J Kidney Dis* 2003; 41(5): 1060-1064.
2. Feinfeld DA, Kaplan R, Dressler R, Lynn RI. Survival of human immunodeficiency virus-infected patients on maintenance dialysis. *Clin Nephrol* 1989; 32(5): 221-224.
3. Ahuja TS, Grady J, Khan S. Changing trends in the survival of dialysis patients with human immunodeficiency virus in the United States. *J Am Soc Nephrol* 2002; 13(7): 1889-1893.
4. Tourret J, Tostivint I, du Montcel ST, *et al.* I. Outcome and prognosis factors in HIV-infected hemodialysis patients. *Clin J Am Soc Nephrol* 2006; 1(6): 1241-1247.
5. Bhagani S, Sweny P, Brook G. Guidelines for kidney transplantation in patients with HIV disease. *HIV Med* 2006; 7(3): 133-139.
6. Gupta SK, Eustace JA, Winston JA, *et al.* Guidelines for the management of chronic kidney disease in HIV-infected patients: recommendations of the HIV Medicine Association of the Infectious Diseases Society of America. *Clin Infect Dis* 2005; 40(11): 1559-1585.
7. Soleymanian T, Raman S, Shannaq FN, *et al.* Survival and morbidity of HIV patients on hemodialysis and peritoneal dialysis: one center's experience and review of the

literature. *Int Urol Nephrol* 2006; 38(2): 331-338.
8. Ahuja TS, O'Brien WA. Special issues in the management of patients with ESRD and HIV infection. *Am J Kidney Dis* 2003; 41(2): 279-291.
9. Centers for Disease Control and Prevention. HIV transmission in a dialysis center – Colombia, 1991-1993. *JAMA* 1995; 274(5): 372-373.
10. Mandayam S, Ahuja TS. Dialyzing a patient with human immunodeficiency virus infection: what a nephrologist needs to know. *Am J Nephrol* 2004; 24(5): 511-521.
11. Rao TK. Human immunodeficiency virus infection in end-stage renal disease patients. *Semin Dial* 2003; 16(3): 233-344.

APPENDIX III: TRANSPLANT REFERENCES

1. Roland ME, Stock PG. Solid organ transplantation is a reality for patients with HIV infection. *Curr HIV/AIDS Rep* 2006; 3(3): 132-138.
2. Terrault NA, Carter JT, Carlson L, Roland ME, Stock PG. Outcome of patients with hepatitis B virus and human immunodeficiency virus infections referred for liver transplantation. *Liver Transpl* 2006; 12: 801-807.
3. Stock PG, Roland ME, Carlson L, *et al.* Kidney and liver transplantation in human immunodeficiency virus-infected patients: a pilot safety and efficacy study. *Transplantation* 2003; 76(2): 370-375.
4. Roland ME, Lo B, Braff J, Stock PG. Key clinical, ethical, and policy issues in the evaluation of the safety and effectiveness of solid organ transplantation in HIV-infected patients. *Arch Intern Med* 2003; 163(15): 1773-1778.
5. Roland ME, Carlson LL, Frassetto LA, Stock PG. Review of solid-organ transplantation in HIV-infected patients. *Transplantation* 2003; 75(4): 425-429.
6. Roland ME, Stock PG. Comprehensive guidelines translate research findings into clinical policy for HIV-infected transplant candidates and recipients. *Enferm Infecc Microbiol Clin* 2005; 23(6): 331-334.
7. Miró JM, Torre-Cisnero J, Moreno A, *et al.* GESIDA/GESITRA-SEIMC, PNS and ONT Consensus Document on Solid Organ Transplant (SOT) in HIV-Infected Patients in Spain (March, 2005). *Enferm Infecc Microbiol Clin* 2005; 23(6): 353-362.
8. Halpern SD, Ubel PA, Caplan AL. Solid-organ transplantation in HIV-infected patients. *N Engl J Med* 2002; 347(4): 284-287.
9. Kumar MS, Sierka DR, Damask AM, *et al.* Safety and success of kidney transplantation and concomitant immunosuppression in HIV-positive patients. *Kidney Int* 2005; 67(4): 1622-1629.
10. Abbott KC, Swanson SJ, Agodoa LY, Kimmel PL. Human immunodeficiency virus infection and kidney transplantation in the era of highly active antiretroviral therapy and modern immunosuppression. *J Am Soc Nephrol* 2004; 15(6): 1633-1639.
11. Neff GW, Bonham A, Tzakis AG, *et al.* Orthotopic liver transplantation in patients with human immunodeficiency virus and end-stage liver disease. *Liver Transpl* 2003; 9(3): 239-247.
12. Ragni MV, Belle SH, Im K, *et al.* Survival of human immunodeficiency virus-infected liver transplant recipients. *J Infect Dis* 2003; 188(10): 1412-1420.
13. Roland ME, Havlir DV. Responding to organ failure in HIV-infected patients. *N Engl J Med* 2003; 348(23): 2279-2281.
14. Roland ME, Adey D, Carlson LL, Terrault NA. Kidney and liver transplantation in HIV-infected patients: case presentations and review. *AIDS Patient Care STDS* 2003; 17(10): 501-507.
15. Samir K, Gupta JA, Eustace JA, *et al.* Guidelines for the Management of Chronic Kidney Disease in HIV-Infected Patients: Recommendations of the H1V Medicine Association of the Infectious Diseases Society of America. *Clin Infect Dis* 2005; 40(11): 1559-1585.
16. Roland ME, Barin B, Carlson L *et al.* HIV-infected liver and kidney transplant recipients: 1 and 3 year outcomes. *Am J Transplant* 2008; 8: 355-365.
17. Michelle E, Roland MD, Bernard L, *et al.* Key clinical, ethical, and policy issues in the evaluation of the safety and effectiveness of solid organ transplantation in HIV-infected patients. *Arch Intern Med* 2003; 163(15): 1773-1778.

APPENDIX IV. DOSAGE OF ANTIRETROVIRAL DRUGS FOR HIV-INFECTED ADULTS WITH CHRONIC KIDNEY DISEASE (CKD) OR RENAL DISEASE (ESRD) (TABLE 3, DIALYSIS REFERENCE 6, GUPTA SK, *et al.*)

Antiretroviral drug, dosing category	Dosage	Rating*	References
Nucleoside reverse transcriptase inhibitors			
Zidovudine†		B-II	[109-116]
Usual dosage	300 mg po bid		
Dosage for patients with CKD or ESRD			
Creatinine clearance ≥15 ml/min	No adjustment		
Creatinine clearance <15 ml/min	100 mg po q 6 - 8 h		
Receiving haemodialysis	100 mg po q 6 - 8 h‡		
Receiving peritoneal dialysis	100 mg po q 6 - 8 h		
Lamivudine†		B-I	[117-119]
Usual dosage	150 mg po bid/300 po qd		
Dosage for patients with CKD or ESRD			
Creatinine clearance ≥50 ml/min	No adjustment		
Creatinine clearance 30 - 49 ml/min	150 mg po qd		
Creatinine clearance 15 - 29 ml/min	150 mg po first dose, then 100 mg po qd		
Creatinine clearance 5 - 14 ml/min	150 mg po first dose, then 50 mg po qd		
Creatinine clearance <5 ml/min	50 mg po first dose, then 25 mg po qd		
Receiving haemodialysis	50 mg po first dose, then 25 mg po qd‡		
Receiving peritoneal dialysis	50 mg po first dose, then 25 mg po qd		
Abacavir§		B-I	[120]
Usual dosage	300 mg po bid/600 mg po qd		
Dosage for patients with CKD or ESRD			
All creatinine clearances	No adjustment		
Receiving haemodialysis	No adjustment‡		
Receiving peritoneal dialysis	Unknown, use with caution		
Stavudine immediate release (IR)		B-II	
Body weight ≥60 kg			
Usual dosage	30 mg po bid		
Dosage for patients with CKD or ESRD			
Creatinine clearance >50 ml /min	No adjustment		
Creatinine clearance 26 - 50 ml/min	20 mg po bid		
Creatinine clearance ≤25 ml/min	20 mg po qd		
Receiving haemodialysis	20 mg po qd‡		
Receiving peritoneal dialysis	Unknown, use with caution		
Body weight <60 kg			
Usual dosage	30 mg po bid		
Dosage for patients with CKD or ESRD			
Creatinine clearance >50 ml/min	No adjustment		

APPENDIX IV. CONTINUED

Antiretroviral drug, dosing category	Dosage	Rating*	References
Creatinine clearance 26 - 50 ml/min	20 mg po bid		
Creatinine clearance ≤25 ml/min	20 mg po qd		
Receiving haemodialysis	20 mg po qd†		
Receiving peritoneal dialysis	Unknown, use with caution		
Body weight <60 kg			
Usual dosage	30 mg po bid		
Dosage for patients with CKD or ESRD			
Creatinine clearance >50 ml/min	No adjustment		
Creatinine clearance 26 - 50 ml/min	15 mg po bid		
Creatinine clearance ≤25 ml/min	15 mg po bid		
Receiving haemodialysis	15 mg po qd†		
Receiving peritoneal dialysis	Unknown, use with caution		
Didanosine buffered tablets		B-II	[123, 124]
Body weight ≥60 kg			
Usual dosage	200 mg po bid		
Dosage for patients with CKD or ESRD			
Creatinine clearance ≥60 ml/min	No adjustment		
Creatinine clearance 30 - 59 ml/min	200 mg po qd		
Creatinine clearance 10 - 29 ml/min	150 mg po qd		
Creatinine clearance <10 ml/min	100 mg po qd		
Receiving haemodialysis	100 mg po qd†		
Receiving peritoneal dialysis	100 mg po qd		
Body weight <60 kg			
Usual dosage	125 mg po bid		
Dosage for patients with CKD or ESRD			
Creatinine clearance ≥60 ml/min	No adjustment		
Creatinine clearance 30 - 59 ml/min	150 mg po qd		
Creatinine clearance 10 - 29 ml/min	100 mg po qd		
Creatinine clearance <10 ml/min	75 mg po qd		
Receiving haemodialysis	75 mg po qd†		
Receiving peritoneal dialysis	75 mg po qd		
Didanosine EC			
Body weight ≥60 kg		B-II	[123-125]
Usual dosage	400 mg po qd		
Dosage for patients with CKD or ESRD			
Creatinine clearance ≥60 ml/min	No adjustment		
Creatinine clearance 30 - 59 ml/min	200 mg po qd		
Creatinine clearance 10 - 29 ml/min	125 mg po qd		
Creatinine clearance <10 ml/min	125 mg po qd		
Receiving haemodialysis	125 mg po qd†		
Receiving peritoneal dialysis	125 mg po qd		
Body weight <60 kg			
Usual dosage	250 mg po qd		
Dosage for patients with CKD or ESRD			
Creatinine clearance ≥60 ml/min	No adjustment		
Creatinine clearance 30 - 59 ml/min	125 mg po qd		
Creatinine clearance 10 - 29 ml/min	125 mg po qd		
Creatinine clearance <10 ml/min	Do not use; use buffered tablets instead		
Receiving haemodialysis	Do not use; use buffered tablets instead		
Receiving peritoneal dialysis	Do not use; use buffered tablets instead		
Emtricitabine		B-II	[127]
Usual dosage	200 mg po qd		
Dosage for patients with CKD or ESRD			
Creatinine clearance ≥50 ml/min	No adjustment		
Creatinine clearance 30 - 49 ml/min	200 mg po q 48 h		
Creatinine clearance 15 - 29 ml/min	200 mg po q 72 h		
Creatinine clearance <15 ml/min	200 mg po q 96 h		
Receiving haemodialysis	200 mg po q 96 h†		
Receiving peritoneal dialysis	Unknown, use with caution		

APPENDIX IV. CONTINUED

Antiretroviral drug, dosing category	Dosage	Rating*	References
Tenofovir		B-II	[128,129]
Usual dosage	300 mg po qd		
Dosage for patients with CKD or ESRD			
Creatinine clearance ≥50 ml/min	No adjustment		
Creatinine clearance 30 - 49 ml/min	300 mg po q 48 h		
Creatinine clearance 10 - 29 ml/min	300 mg po q 72 h		
Receiving haemodialysis	300 mg po every 7 days‡		
Receiving peritoneal dialysis	Unknown, use with caution		
Emtricitabine/tenofovir		C-III	[130]
Usual dosage	200 mg/300 mg po qd		
Dosage for patients with CKD or ESRD			
Creatinine clearance ≥50ml/min	No adjustment		
Creatinine clearance 30 - 49 ml/min	One tab po q 48 h		
Creatinine clearance <30 ml/min	Unknown, should not use combination tablet		
Non-nucleoside reverse transcriptase inhibitors			
Nevirapine		B-II	[131-135]
Usual dosage	200 mg po bid		
Dosage for patients with CKD or ESRD			
Creatinine clearance >20 ml/min	No adjustment		
Receiving haemodialysis	No adjustment‡		
Receiving peritoneal dialysis	Unknown, use with caution		
Efavirenz		C-III	[136-138]
Usual dosage	600 mg po qd		
Dosage for patients with CKD or ESRD	No adjustment		
Delavirdine		C-III	[139]
Usual dosage	400 mg po tid		
Dosage for patients with CKD or ESRD	No adjustment		
Protease inhibitors			
Indinavir		C-III	[140, 141]
Usual dosage	800 mg po tid		
Dosage for patients with CKD or ESRD	No adjustment		
Saquinavir soft gel		C-III	[132, 142, 143]
Usual dosage	1 200 mg po tid		
Dosage for patients with CKD or ESRD	No adjustment		
Saquinavir hard gel		C-II	[132, 142, 144]
Usual dosage	600 mg po tid		
Dosage for patients for CKD or ESRD	No adjustment		
Nelfinavir		C-III	[133, 145, 146]
Usual dosage	1 250 mg po bid		
Dosage for patients with CKD or ESRD	No adjustment		
Amprenavir		C-III	[147]
Usual dosage	1 200 mg po bid		
Dosage for patients with CKD or ESRD	No adjustment		
Fosampenavir		C-III	[148]
Usual dosage	1 400 mg po qd/700 mg po bid		
Dosage for patients with CKD or ESRD	No adjustment		
Ritonavir		C-III	[135, 142, 149]
Usual dosage	600 mg po bid		
Dosage for patients with CKD or ESRD	No adjustment		
Lopinavir/ritonavir		C-III	[150, 151]
Usual dosage	400 mg/100 mg po bid		
Dosage for patients with CKD or ESRD	No adjustment		
Atazanavir		C-III	[152]
Usual dosage	400 mg po qd		
Dosage for patients with CKD or ESRD	No adjustment		

APPENDIX IV. CONTINUED

Antiretroviral drug, dosing category	Dosage	Rating*	References
Entry/fusion inhibitors			
Enfuvirtide		B-II	[153]
Usual dosage	90 mg sc bid		
Dosage for patients with CKD or ESRD			
Creatinine clearance ≥35 ml/min	No adjustment		
Creatinine clearance <35 ml/min	Unknown, use with caution		

*The rating is for the recommendations on dose adjustment for patients with reduced renal function.

†Zidovudine/lamivudine (Combivir; GlaxoSmithKline) should be administered as separate component medications in patients with creatinine clearance <50 ml/min.

‡Administer either the daily dose or one of the daily doses after haemodialysis.

§Zidovudine/lamivudine/abacavir (Trizivir; GlaxoSmithKline) and lamivudine/abacavir (Epzicom; GlaxoSmithKline) should be administered as separate component medications in patients with creatinine clearance <50 ml/min.

CASE STUDY

THE UTILITY OF PHARMACY DISPENSING DATA FOR ART PROGRAMME EVALUATION AND EARLY IDENTIFICATION OF PATIENT LOSS TO FOLLOW-UP

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The rapid scale-up of antiretroviral treatment (ART) programmes in sub-Saharan Africa has challenged the capacities of ART services to monitor and retain large numbers of patients within programmes effectively. Many ART clinics in sub-Saharan Africa now have to cope with patient complements of several thousands,[1-3] all of whom require monitoring and tracking. Initially, programme emphasis was placed on the maintenance of high levels of adherence to therapy, particularly because of the concerns of widespread viral resistance that could develop as a result of expanded access to ART in low- and middle-income countries (LMICs).[4] The public health approach to delivery of ART therefore recognised the need for adherence strategies as an essential component of individual and programmatic treatment success.[5] The South African ART guidelines included protocol provision for adherence counselling strategies within clinics.[6] Despite initial scepticism, the feasibility of expanded access in LMICs has been justified by many early programmes reporting high levels of adherence[7,8] and viral suppression rates which were comparable with those achieved in industrialised settings.[9] While these results were encouraging, they represented the successful outcomes of individuals having been retained within the programmes, largely ignoring those individuals lost to each programme. However, overall programme performance and population impact may be more accurately reflected by intention-to-treat (ITT) rather than on-treatment analysis (OTA). The differences between ITT and OTA results may be considerable, and a recent meta-analysis has highlighted that the loss to follow-up after initiating ART is a major problem facing large-scale ART roll-out programmes in sub-Saharan Africa.[10]

RETENTION

The result of a systematic review of attrition within sub-Saharan African ART programmes on the proportion of adult patients remaining in care and on ART at 6 months or longer between 2000 and 2007 has been reported.[10] The analysis was based on data from 32 journal articles and conference abstracts describing 74 192 patients in non-research ART programmes in 13 countries. Retention was defined as the proportion of individuals known to be alive and receiving ART at the end of each follow-up period, and included those transferred to other programmes. Attrition was defined as the proportion of those not retained, and was a composite measure comprising losses owing to death of 40%, losses to follow-up of 56%, and discontinuation of ART within the programme of 4%. Weighted mean retention rates, as reported, were 79.1%, 75.0% and 61.6% at 6, 12 and 24 months, respectively. Of those reporting 24 months of follow-up, the best programme retained 85%, and the worst retained 46%, of patients. Attrition was higher in those studies with shorter reporting periods, with monthly weighted mean attrition rates of 3.3%, 1.9% and 1.6% per month for studies reporting to 6, 12 and 24 months, respectively. As those programmes reporting high attrition were least likely to provide data beyond 6 months, this was felt by the authors to indicate that overall patient retention had been overestimated in the published reports. The main conclusion was that overall attrition in African ART programmes was very high (40%) and was predominantly the result of loss to follow-up and, to a lesser degree, death. The authors concluded that there was a need for better patient trac-

ing procedures, increased understanding of loss to follow-up, and earlier initiation of ART in order to reduce mortality. As retention varied widely across programmes, it was felt that those programmes that had achieved higher retention rates might serve as models for future improvements.

CONVENTIONAL DATA SOURCES

Conventional approaches to data collection are 'doctor-centred', relying on patient information captured on data capture forms which are subsequently entered into a computerised database by a data entry clerk for subsequent use for programme evaluation (Fig. 1). More sophisticated versions incorporate direct entry of medical information into an electronic medical record (EMR) where the data are available for both patient care and programme evaluations. However, EMRs require computer networks and ongoing IT support which is frequently not available in many peripheral and community ART clinics. The rapid scale-up of ART to millions of patients, the scarcity of doctors and pharmacists, a poor computer infrastructure and involvement of nurses and lay counsellors in patient care both inside and outside of formal clinics, compound the difficulties of data collection and collation. Furthermore, doctor visits are typically scheduled 6-monthly,[6] which does not allow early detection of attrition from the programme as patients might have been off therapy for several months before being identified.

MINIMUM DATA REQUIREMENTS FOR ITT ANALYSES

Data for programme evaluation of retention differs from that required for individual patient management and is therefore not just a consolidation of individual responses to ART. ITT analysis of programme performance necessitates knowledge of the numbers of individuals initiating therapy, remaining on therapy, and lost (attrition) to the programme. Further classification of attrition into known deaths, transfers and remaining loss to follow-up requires additional active follow-up procedures. Establishment of vital status may be difficult to achieve within a normal clinic, and may be better achieved in those services that have established interactions with patients at a community level.

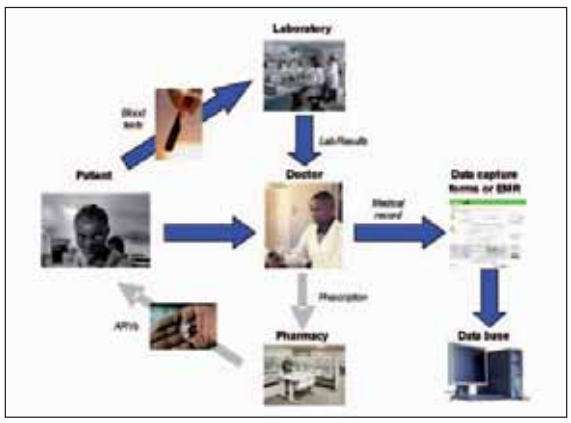

Fig. 1. The data collection cycle.

PHARMACY-BASED DATA SOURCES

Pharmacy-based records have previously been reported to be a simple and effective population-level tool for monitoring adherence within scaling-up African HAART programmes.[11] Pharmaceutical dispensing already requires the capturing of date information, patient identifiers such as age, and gender and contact details together with specifics of the prescription instructions from the health care provider. ART programmes may also easily add a requirement for justification of regimen changes classified into simple categories such as intolerance, toxicity or virological failure. If the date and time of patient receipt of ARVs could be captured, the pharmacy-based records could be expanded to capture programme retention data as well as adherence information. Most of these data are required to be collected as part of routine pharmacy functioning in all treatment sites and can be made available for programme evaluation without adding to the workload of busy clinics.

iDART SYSTEM

As an extension of the concept of using pharmacy information as a programme evaluation tool, the intelligent dispensing of ART system (iDART) has been developed as a non-proprietary programme. iDART is a pharmacy application developed on open-source software that allows dispensing of ART both on site and from a remote pharmacy. The system has been developed in response to a need to manage large numbers of patients on ART simply and effectively. The key benefits of the iDART system are accurate tracking of patient treatment and providing comprehensive patient treatment history. Operationally, iDART aids accurate ARV stock control management and faster pharmacy dispensing through faster processing. It reduces and identifies loss of ARVs, and it operates through clearly identifiable, multilingual bar-coded labels which are created for each and every drug and patient package. iDART provides a pharmacy management tool incorporating stock-control, drug deliveries and drug-dispensing information designed to allow a central pharmacist to provide services to multiple satellite clinics (Fig. 2). Demographic details, regimen dispensed and date and time of receipt of ART by the patient are captured without the need for additional data clerks (Table I). Standardised programme reports can be generated for funding agencies (e.g. PEPFAR) and health authorities (Fig. 3), together with updated lists of patients who have failed to pick up their prescriptions and who are defaulting from the programme. The programme has already been successfully used in 7 large ART clinics in North West, Gauteng, Western Cape and Northern Cape provinces and has been integrated with other data systems (e.g. EMR, lab-based) and the Western Cape provincial health record system (eKAPA). One of the most important

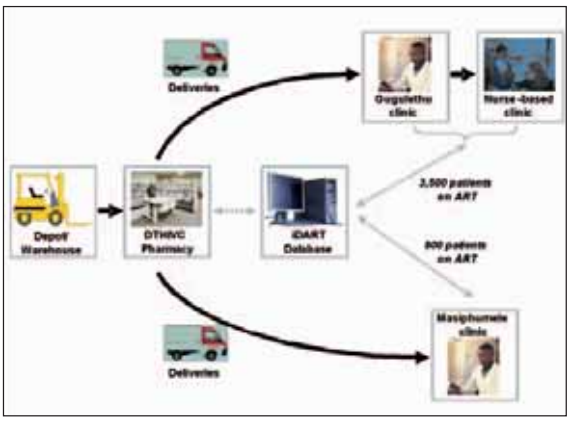

Fig. 2. The iDart system as applied to Gugulethu and Masiphumelele clinics.

functions of iDART lies in the various reports that the software makes available. These range from basic stock control management and monitoring reports to specific patient defaulter lists, which facilitates easy management and follow-up of patients. iDART also keeps the entire patient history of a patient in its database, providing accurate tracking of patients receiving treatment from ART sites (Fig. 4). The iDART system also allows the decanting of packages to remote clinics and dispensaries that do not hold stock of ARVs; a central pharmacy prepares packages for patients belonging to remote clinics and the system will trace the entire process until the patients collect their drugs. Feedback is then provided via the network or other data transfer systems to the central pharmacy to signal that the package was collected, and the pharmacist is then allowed to package drugs

Fig. 3. An iDart programme report.

Fig. 4. An iDart clinic report.

for the patient in the next month. Minimum system requirements are a single computer, barcode printer and barcode reader. Data transfer can utilise a flash memory stick, cell phone, email or internet connection.

CAPE TOWN iDART CONFORMATION

The Cape Town central pharmacy receives and manages drug deliveries and supports peripheral clinics (Fig. 2). A single pharmacist and pharmacy assistant dispense ARVs to 2 peripheral clinics. Gugulethu is a busy doctor-based ARV clinic servicing >3 500 patients, which incorporates a nurse-led decanting clinic for patients established on stable ARVs. Masiphumelele is a smaller public-sector community polyclinic providing >800 patients with ARVs with both doctor- and nurse-led services. Gugulethu and Masiphumelele are approximately 20 and 40 kilometres distant from the pharmacy, respectively, with data transfer between peripheral site networks and central database via a virtual private network (vpn).

SIZOPHILA COMMUNITY ADHERENCE PROGRAMME

The Gugulethu ARV service is supported by a network of adherence counsellors who are recruited from the community, openly live with HIV and are trained and employed to carry out both clinic- and community-based services (Fig. 5). On any weekday, there are counsellors who report to the clinic in the morning and perform the clinic duties which include treatment readiness sessions for new recruits, adherence trouble-shooting for established patients and day-to-day clinic operations.

TABLE I. INFORMATION CAPTURED FROM PHARMACY AND DISPENSING INPUTS TO iDART AND INDIVIDUAL PATIENT AND CONSOLIDATED PROGRAMME REPORT OUTPUTS

iDART inputs	Information captured	Outputs
ARVs delivered ARV returns ARV expirations ARVs dispensed ARVs transferred to clinics	ARVs in stock ARVs dispensed	Pharmacy stock control ARV regimens used
Registration of patient Date receipt of 1st ARVs Date of repeat ARVs Failure to pick up ARVs	Demographic details Start date on ART Duration of treatment List of defaulters	Programme reports Individual adherence Individual retention

Fig. 5. Adherence counsellors are recruited from the community, and are trained and employed to carry out clinic- and community-based services.

The majority of the team work daily from home, their clients having been assigned geographically. They attend to home visits for new recruits as well as regular visits for defaulters and patients with adherence problems (red alert patients). Patients who adhere poorly, as indicated by pill counts, and patients who are not virally suppressed, are classified as 'red alert' and referred to their relevant counsellor for increased attention. A defaulters list is also generated from the iDART pharmacy system, based on missed pharmacy pick-up dates, and these patients are followed up by their counsellors. Adherent patients are classified as 'green' patients and visited less frequently. They attend the clinic 2-monthly for new drug supply and are seen by a nurse practitioner or doctor every 4 months. Each counsellor is responsible for approximately 120 patients, of whom only the minority are 'red alert'. Clinic-based activities ensure that patients are well informed about the need for treatment and programme adherence and, together with the red alert system, this ensures patient adherence, excellent viral suppression rates and thus sustained therapy options. However, it is the field-based activities of the counsellors providing individualised support, home visits and regular follow-up that ensure ongoing adherence and excellent retention with reliable outcome data. iDART is an important trigger for the adherence/retention team that patients have defaulted treatment pick-up, resulting in immediate community follow-up by the relevant counsellor. This combination of clinic- and field-based counsellors together with iDART maintains excellent adherence and viral suppression rates as well as remarkably low loss-to-follow-up rates in this large community-based clinic in Gugulethu, Cape Town.

CONCLUSIONS

Pharmacy pick-up data by patients are well suited for identification of patients retained or those potentially lost to the programme. iDART is a flexible solution able to be implemented on a variety of IT platforms. Alone, it is a simple solution which can be implemented at peripheral clinic sites by pharmacy management, enabling standard report generation including early identification of programme losses, and it enables implementation of active community follow-up strategies.

As iDART has been developed on open source software which is free and requires no licence, the full pharmacy management system is available for implementation at any antiretroviral clinic and can be downloaded online at URL <http://www.cell-life.org/content/view/75/>.

REFERENCES

1. Stringer JS, Zulu I, Levy J, *et al.* Rapid scale-up of antiretroviral therapy at primary care sites in Zambia: feasibility and early outcomes. *JAMA* 2006; 296(7): 782-793.
2. Dalal RP, Macphail C, Mqhayi M, *et al.* Characteristics and outcomes of adult patients lost to follow-up at an antiretroviral treatment clinic in Johannesburg, South Africa. *J Acquir Immune Defic Syndr* 2008; 47(1): 101-107.
3. Bekker LG, Myer L, Orrell C, Lawn S, Wood R. Rapid scale-up of a community-based HIV treatment service: programme performance over 3 consecutive years in Guguletu, South Africa. *S Afr Med J* 2006; 96(4): 315-320.
4. Harries AD, Nyanguku DS, Harries AD, *et al.* Preventing antiretroviral anarchy in Africa. *Lancet* 2001; 358: 410-414.
5. Scaling up antiretroviral therapy in resource-limited settings: Treatment guidelines for a public health approach. 2003 revision. Geneva: World Health Organization. http://www.who.int/hiv/pub/prev_care/en/arvrevision2003en.pdf (accessed 10 April 2008).
6. South African National Antiretroviral Treatment Guidelines. Pretoria: National Department of Health, 2004. http://www.hst.org.za/uploads/files/sa_ART_Guidelines1.pdf (accessed 10 April 2008).
7. Orrell C, Bangsberg DR, Badri M, Wood R. Adherence is not a barrier to successful antiretroviral therapy in South Africa. *AIDS* 2003; 17(9): 1369-1375.
8. Mills EJ, Nachega JB, Buchan I, *et al.* Adherence to antiretroviral therapy in sub-Saharan Africa and North America. *JAMA* 2006; 296(6): 679-690.
9. Ivers LC, Kendrick D, Doucette K. Efficacy of anti-retroviral therapy programs in resource-poor settings: a meta-analysis of the published literature. *Clin Infect Dis* 2005; 41: 217-224.
10. Rosen S, Fox MP, Gill CJ. Patient retention in antiretroviral therapy programs in sub-Saharan Africa: A systematic review. *Plos Med* 2008; 4(10): e298.
11. Nachega JB, Hislop M, Dowdy DW, *et al.* Adherence to highly active antiretroviral therapy assessed by pharmacy claims predicts survival in HIV-infected South African adults. *J Acquir Immune Defic Syndr* 2006; 43(1): 78-84.

CLINICAL

SHORT-TERM EFFECTIVENESS AND SAFETY OF HAART IN THE FORM OF A GENERIC FIXED-DOSE COMBINATION OF STAVUDINE, LAMIVUDINE AND NEVIRAPINE (TRIVIRO) IN HIV-1-INFECTED ADULTS IN ZIMBABWE

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Objectives. To assess the effectiveness and safety of a twice-daily regimen of a generic fixed-dose combination (FDC) of stavudine, lamivudine and nevirapine (Triviro) in a cohort of Zimbabwean HIV-1-positive adults.

Design. A prospective, open-label, one-arm study of antiretroviral-naïve adults with CD4 counts <200 cells/µl. Fifty-three intention-to-treat (ITT) patients were enrolled and monitored for 4 months.

Setting. Three primary health care facilities in Zimbabwe.

Outcome measures. Efficacy criteria included plasma HIV-1 RNA load, CD4 counts, patient weight and Karnofsky performance scores. Toxicity was assessed by clinical evaluation and laboratory tests.

Results. There was a significant 3.0 $\log_{10}$ decrease in viral load at weeks 8 and 16 for both groups. Viral loads ≤400 copies/ml were achieved in 96% of per protocol (PP) and 85% of ITT patients at 8 and 16 weeks. At 4 months 85% of the PP group and 76% of the ITT group achieved undetectable viral loads. There was a significant increase in median CD4 counts of 101 cells/µl for PP and 86 cells/µl for the ITT analysis. The number of PP patients with Karnofsky scores of 100 improved from 10 (21%) to 38 (81%) and BMI increased by an average of 1.15 kg/m^2. Of the 134 adverse events recorded, 4 (3%) were severe. Of 16 adverse drug reactions in 10 patients, 13 were ascribed to nevirapine. One adverse reaction resulted in withdrawal from the study.

Conclusion. The effectiveness and safety of Triviro was comparable to that seen with other formulations, and our results support the use of this FDC in Zimbabwe and elsewhere.

The success of HIV/AIDS treatment depends on the effective and appropriate use of antiretroviral agents (ARVs). Resource-limited countries bear the brunt of this public health crisis, and their responses necessarily differ from those of industrialised nations. Ideally, ARV administration and patient monitoring in public programmes should be standardised, with free, effective, tolerable drugs and simple regimens to promote patient compliance.

Most developing countries employ the World Health Organization (WHO) public health approach to antiretroviral treatment, which aims to maximise patient survival using highly active antiretroviral therapy (HAART) with a combination of three agents from different drug classes in order to enhance efficacy and minimise the development of resistance through the promotion of adherence.[1]

Adherence to treatment programmes is of particular importance to prevent treatment failure and development of drug resistance, since patient monitoring and availability of alternative drugs is often limited in resource-limited countries. Patient compliance in these countries has been found to be at least as good as that in developed regions,[2] but obstacles to long-term adherence include medication cost and affordability in the health care setting, access to treatment, side-effects and the complexities of treatment schedules.

Companies producing generic drugs were the first to market fixed-dose combination (FDC) ARV preparations, and these drugs have won broad acceptance in the developing world. A study by Chien in 2007 showed that the vast majority of first-line ARV drugs in sub-Saharan Africa are supplied by generic companies.[3] This is in large part due to the fact that the average price of generic drugs is usually a fraction of that of brand-name equivalents. FDCs comprise a third of the drugs purchased in the region, with the stavudine/lamivudine/nevirapine (d4T/3TC/NVP) combination constituting the largest proportion at 20%. FDCs form an important pillar in promoting adherence, since they greatly reduce pill burden, dosing frequency and prescription errors. As with brand-name drugs, generic formulations are subject to stringent quality control standards. However, in order to ensure patient safety and public support, it is essential to ensure that counterfeit generic or brand name drugs do not find their way onto the market.

The Triviro (d4T/3TC/NVP) (Ranbaxy Laboratories, Centurion, South Africa) combination HAART is similar in formulation to Triomune (Cipla, Mumbai, India) and GPO-VIR (Thai Government Pharmaceutical Organisation). It has been shown to be comparable both in terms of bioequivalence[4] and safety[5] to each of its components.

While several studies have been conducted in Central and West Africa using d4T/3TC/NVP,[6,7] few have reported the use of this FDC in the southern African region. Zimbabwe has one of the highest HIV prevalence rates in southern Africa, which in 2005 was estimated at 33% in adults aged 15 - 49.[8]

This study was designed to evaluate the short-term effectiveness and safety of Triviro in an eligible cohort of HIV-1-positive patients in Zimbabwe. The goals were to assess virological, immunological and clinical improvement, tolerability and safety profile in treatment-naïve participants.

METHODS

This prospective, open-label, one-arm observational study was conducted at three primary health care facilities in Zimbabwe (Zimbabwean Swiss AIDS Care Foundation, the Colin Saunders Hospital and the Well Women's Clinic). Enrolment took place from May 2005 until February 2006.

The enrolment criteria for patients who qualified were: >18 years of age, HIV-1 positive at WHO stage I, II or III with CD4 counts <200 cells/µl or advanced WHO stage III disease presenting with recurrent or persistent oral thrush and/or recurrent invasive bacterial infections irrespective of CD4 count. Exclusion criteria were inability to provide informed consent, a history of hypersensitivity to treatment components, alcohol or drug abuse, active pulmonary tuberculosis, acute/active opportunistic infections, a history of previous ARV therapy, pregnancy or breastfeeding, female patients not using contraception, evidence of peripheral neuropathy, haemoglobin concentration <9.0 g/dl, platelet count <75 000×10^9/l, aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥3 times the upper limit of normal (ULN), serum creatinine ≥1.6 times the ULN, serum amylase ≥1.6 times the ULN, total bilirubin ≥30 µmol/l, and malabsorption or severe chronic persistent diarrhoea.

Informed consent was obtained from all participants. The Medicines Control Authority of Zimbabwe approved the protocol and provided a provisional licence for the use of Triviro before the study was conducted.

Two fixed-dose tablet formulations were considered for use as study medication: Triviro-30 (150 mg 3TC, 30 mg d4T and 200 mg NVP) for patients with a body weight <60 kg and Triviro-40 (150 mg 3TC, 40 mg d4T and 200 mg NVP) for patients with a body weight >60 kg. This study was performed before revision of the WHO guidelines on stavudine dosing, where 30 mg stavudine is the recommended dose regardless of body weight.[9]

A 2-week nevirapine lead-in dose was used to assess tolerability of the formulation, especially nevirapine, and to decrease the risk of adverse reactions. During this period patients were provided with a single tablet of Triviro-30 or Triviro-40 for administration in the morning and a single tablet of Coviro LS 30 or 40, a stavudine/lamivudine nucleoside combination, in the evening that corresponded with the dose of stavudine in the Triviro formulation. Patients who experienced no significant drug-related adverse events were advanced to therapy with Triviro-30 or Triviro-40 twice daily after the initial 2-week treatment period.

Patients were excluded from the study if they were lost to follow-up (failure to visit clinic within a week of scheduled follow-up visit), or experienced serious intolerable adverse events or clinical deterioration indicative of viral resistance. Treatment of other ailments was continued unless contraindicated for concomitant use in combination with the study medication.

Patient monitoring was performed within 2 weeks of treatment initiation to establish drug tolerability. Thereafter follow-up assessments at 4 weeks, 8 weeks and 4 months were performed. CD4 counts were measured at baseline and 4 months. HIV-1 RNA viral load testing was performed at baseline, 8 weeks and 4 months. Karnofsky scoring was assessed at baseline and 4 months. Potential toxicity of the study medication was assessed by clinical examination and monitoring of levels of haemoglobin, white blood cells and platelets assessed at the screening visit, week 8 and month 4. Serum transaminases were measured at the screening visit, 2, 4 and 8 weeks and 4 months. Serum creatinine and amylase were measured at screening, week 2 and month 4. The Aids Clinical Trials Group (ACTG) rating was used to assess toxicity.[10]

LABORATORY ASSAYS

All HIV viral load and CD4 measurements were performed by the laboratory of Vermaak and Partners, Pretoria, South Africa. The Nuclisens EasyQ HIV-1 assay (bioMerieux, Marcy l'Etiole, France) was used for viral load measurements.

STATISTICS

Viral loads and CD4 cell counts were summarised using descriptive statistics. Changes in the medians of viral loads (using $\log_{10}$ transformation) and CD4 cell counts relative to baseline were tested for significance using the Wilcoxon signed rank test. Proportions of subjects with plasma HIV-1 RNA levels ≤25, <50 and <400 copies/ml were assessed using the binomial (exact) 95% confidence interval. Changes in blood pressure, body mass index (BMI), pulse rate, respiratory rate, temperature and haemoglobin were analysed using Student's paired *t*-test. Changes in median serum aspartate transaminase, alanine transaminase, bilirubin, serum creatinine, serum amylase, white cell counts, platelet counts and Karnofsy score were tested for significance using the Wilcoxon signed rank test. The proportion of patients who had a Karnofsky score of 100 at baseline and at month 4 was also summarised. Missing data were replaced with the last available observation for CD4 cell count and viral load data. Statistical analysis was performed using PC SAS 8.2 (SAS Institute Inc., Cary, NC) at 5% two-sided alpha levels.

RESULTS

Out of 55 patients screened, 53 were enrolled at three participating primary health care clinics in Zimbabwe. Of this intention-to-treat (ITT) group (i.e. patients who received at least 1 dose of drug), 6 patients withdrew or were excluded from the study due to: adverse events (2), non-compliance (2), loss to follow up (1) and failure to attend the clinic (1). One of the 2 patients who withdrew as a consequence of reported adverse events presented with immune reconstitution syndrome (tuberculosis) and died 2 weeks after withdrawal from the study, and the other presented with a severe rash thought to be caused by nevirapine. The demographics of the ITT group are shown in Table I.

TABLE I. DEMOGRAPHIC CHARACTERISTICS OF THE ITT GROUP AT BASELINE

Variable	Statistics
Age (yrs)	
N	53
Mean±SD	41.6±7.63
Min, max	28.6, 56.4
Sex (*N* (%))	
Female	27 (50.9%)
Male	26 (49.1%)
Race (*N* (%))	
Black	48 (90.6%)
Caucasian	2 (3.8%)
Mixed race	3 (5.7%)
Viral load	2 700
CD4	117

VIRAL AND IMMUNOLOGICAL RESPONSE

There was a significant decrease in HIV-1 RNA levels from the median (interquartile range (IQR)) at baseline of 4.4 $\log_{10}$ copies/ml to 1.4 $\log_{10}$ copies/ml (3.0 $\log_{10}$ decrease) at week 8, which was maintained at month 4, for both ITT and PP (i.e. patients who followed the study protocol strictly) groups (p<0.0001) (Table II). The proportion of patients with viral loads of ≤400 copies/ml was 96% in the PP group and 85% in the ITT group at both 8 and 16 weeks of treatment. These results are presented in Table III and Fig. 1. At 4 months, 87.2% of the PP group had viral RNA levels ≤50 copies/ml, with 85.1% achieving undetectable levels (≤25 copies/ml). Of the ITT group, 77.4% had viral loads ≤50 copies/ml and 75.5% ≤25 copies/ml (Table III).

TABLE II. VIRAL LOAD, $\log_{10}$ (HIV RNA COPIES/ml) FOR ITT AND PP POPULATIONS AT BASELINE, WEEK 8 AND MONTH 4

	Baseline		Week 8		Month 4	
Statistic	ITT	PP	ITT	PP	ITT	PP
N	53	47	53	46*	53	47
Median	4.431	4.3979	1.398	1.3979	1.398	1.3979
IQR (Q1 - Q3)	4.2041 - 4.9085	4.1139 - 4.8195	1.3979 - 1.9638	1.3979 - 1.6435	1.3979 - 1.3979	1.3979 - 1.3979

*Data for 1 subject not available.

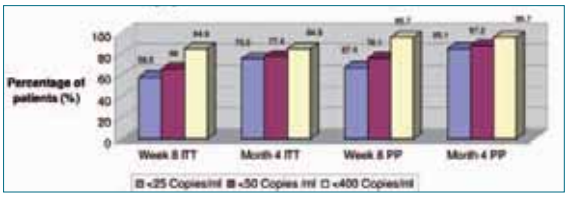

Fig. 1. Viral loads in the ITT and PP groups at week 8 and month 4.

A significant improvement in the CD4 cell counts from baseline to month 4 was observed, with an increase in the median count of 86 cells/µl for the ITT group and 101 cells/µl for the PP group (Fig. 2).

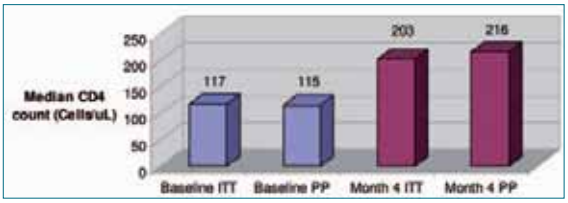

Fig. 2. CD4 counts for ITT and PP populations at baseline and month 4.

PHYSIOLOGICAL PARAMETERS

Participant body weight increased significantly after 4 months of treatment in the PP group, with a mean increase in weight of 3.22 kg, corresponding to a BMI increase of 1.15 kg/m^2. Respiratory rate decreased significantly from baseline (an average decrease of 1.3 breaths/min), while blood pressure, pulse rate and temperature remained essentially unchanged. The Karnofsky performance score at 100 was found to markedly improve in the PP group from 10 patients (21.3%) at baseline to 38 (80.9%) at the conclusion of the study.

TOLERABILITY

Laboratory analyses of markers to potentially indicate toxicity was performed. AST levels were shown to decrease 2 weeks after initiation of treatment, but approached baseline levels at later visits. ALT levels were elevated at month 4, and serum creatinine was increased at week 2. Amylase was shown to decrease at month 4, while significant declines in bilirubin were seen at all time points. While the median and IQR values for all the enzymatic parameters did not exceed grade 1 according to the ACTG guidelines,[10] there were instances where the maximum values were indicative of grade 2 or 3. A single patient had AST and ALT levels in the grade 2 (2.6 - 5.0 times ULN) range at screening, which decreased to below threshold during treatment. Another patient showed elevated levels of AST and ALT (grade 3; 5.1 - 10 times ULN) at week 8, which fell to normal at week 16. Serum creatinine levels were within the grade 1 (1.1 - 1.3 times ULN) range, except for 1 patient at grade 2 (1.4 - 1.8 times ULN) at 2 weeks, which normalised by 16 weeks. Analysis of amylase levels showed 4 patients at grade 2 (1.1 - 1.5 times ULN) and grade 3 (1.6 - 2.0 times ULN), respectively. This changed to 5 patients at grade 2 and 1 at grade 3 at 16 weeks. One patient had a grade 3 (2.6 - 5.0 times ULN) bilirubin level at week 4, which normalised by week 16. Although slightly elevated levels of haemoglobin and platelets were noted at 4 months, no changes were seen in the lymphocyte counts.

ADVERSE EVENTS AND DRUG REACTIONS

One hundred and thirty-four adverse events were recorded, the commonest being headache in 6 patients (11.3%), diarrhoea in 5 (9.4%), cough in 4 (7.5%), and loss of appetite and vomiting in 3 (5.7%). The majority (74.6%) of these events were judged to be mild, with 22.4% moderate and 3% severe. Eighty-one per cent of these events were considered to be unrelated to the study medication, 3.7% to have a remote possibility of causal relatedness, 11.9% a possible connection and 3% a probable connection. More than 1 adverse event was noted in 40 patients (76%). Sixteen adverse drug reactions were noted in 10 patients, of which 13 were ascribed to nevirapine (81.3%) and 3 (18.8%) to stavudine. The majority (56.3%) of these reactions were mild, 37.5% were moderate, and there was one instance (6.3%) of a severe rash that resulted in withdrawal from the study.

DISCUSSION

In this observational study of Triviro usage in Zimbabwe, we found effective viral suppression and immunological recovery at month 4 after initiation of generic FDC HAART in the majority of the participants. A significant virological improvement after 4 months was noted, with a 3.0 $\log_{10}$ decline in the median HIV-1 RNA levels from

TABLE III. NUMBER (%) OF ITT AND PP PATIENTS WITH VIRAL LOADS ≤25, ≤50 AND ≤400 COPIES/ml AT WEEK 8 AND MONTH 4

	Week 8		Month 4	
	ITT	PP	ITT	PP
≤25 copies/ml 95% CI	31 (58.5%) 44.1 - 71.9%	31 (67.4%) 52.0 - 80.5%	40 (75.5%) 61.7 - 6.2	40 (85.1%) 71.7 - 93.8%
p-value†	0.2164	0.0183*	0.0002**	<0.0001**
≤50 copies/ml 95% CI	35 (66.0%) 51.7 - 78.5%	35 (76.1%) 61.2 - 7.4%	41 (77.4%) 63.8 - 87.7%	41 (87.2%) 74.3 - 95.2%
p-value†	0.0195*	0.0004**	<0.0001**	<0.0001**
≤400 copies/ml 95% CI	45 (84.9%) 72.4 - 93.3%	44 (95.7%) 85.2 - 99.5%	45 (84.9%) 72.4 - 93.3%	45 (95.7%) 85.5 - 99.5%
p-value†	<0.0001**	<0.0001**	<0.0001**	<0.0001**

*Significant at 5% level, **Significant at 1% level.
†Two-sided binomial test (H_0: proportion = 0.5).

baseline. Similarly, a significant immunological improvement was seen, with an average increase of 101 CD4 cells/µl for the PP-treated group. These results compare favourably with, and in some cases exceed, the endpoints of similar studies.[6,7] Patient well-being was also found to be enhanced, with a marked increase in BMI and in the number of patients with a Karnofsky score of 100 by the end of 4 months. The majority of adverse events were not judged to be severe, although there was one withdrawal due to debilitating rash. The adverse drug reactions observed were also typical for the drugs used, and are mentioned in the product information.

The d4T/3TC/NVP FDC used in this study has previously been used as HAART therapy for advanced AIDS care[11] and is increasingly being used for paediatric treatment, with oral formulations facilitating easier dosage and increased compliance.[12] Although adult trials have been performed using d4T/3TC/NVP formulations in other regions, few studies have been performed in southern Africa. The reports to date are on the use of the combination for the treatment of AIDS-associated Kaposi's sarcoma in KwaZulu-Natal, South Africa[13] and for prevention of vertical transmission of HIV-1 in Mozambique,[14] and an initial report of its use in adults in South Africa.[15]

The present study has some limitations. A longer-term study is needed to establish toxicity in patients using what could be lifelong treatment, especially given reports from Thailand of metabolic complications such as dyslipidaemia.[16] Testing for resistance was not performed in our study, but will become critical in light of cross-resistance that has been described in second-line treatment-naïve patients failing the d4T/3TC/NVP treatment.[17]

The positive longer-term experiences of other sites with Triomune[18,19] and Triviro[20] suggest that use of these generic HAART FDCs in southern Africa could be considered as first-line therapy.

In conclusion, our short-term results support the use of Triviro, and d4T/3TC/NVP FDCs in general, to treat HIV-1 positive adults.

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REFERENCES

1. Gilks CF, Crowley S, Ekpini R, *et al.* WHO public-health approach to antiretroviral treatment against HIV in resource-limited settings. *Lancet* 2006; 368: 505-510.
2. Mills EJ, Nachega JB, Buchan I, *et al.* Adherence to antiretroviral therapy in sub-Saharan Africa and North America. *JAMA* 2006 296: 679-690.
3. Chien CV. HIV/AIDS drugs for sub-Saharan Africa: how do brand and generic supply compare? *PLoS ONE* 2007; 2: e278.
4. Monif T, Tippabhotla SK, Garg M, Singla AK, Vijan T. Nevirapine/lamivudine/stavudine as a combined-formulation tablet: bioequivalence study compared with each component administered concurrently under fasting condition. *Int J Clin Pharmacol Ther* 2006; 44: 276-283.
5. Marier JF, Dimarco M, Guilbaud R,*et al.* Pharmacokinetics of lamivudine, zidovudine, and nevirapine administered as a fixed-dose combination formulation versus coadministration of the individual products. *J Clin Pharmacol* 2007; 47: 1381-1389.
6. Laurent C, Kouanfack C, Koulla-Shiro S, *et al.*Effectiveness and safety of a generic fixed-dose combination of nevirapine, stavudine, and lamivudine in HIV-1-infected adults in Cameroon: open-label multicentre trial. *Lancet* 2004; 364: 29-34.
7. Jarrousse B, Ba M, Dakouo ML, *et al.* Fixed-dose combination of stavudine 30 mg/lamivudine/nevirapine as standard first-line regimen in a sub-Saharan cohort of HIV-1 infected adult patients. XVI International AIDS Conference, Toronto, Canada, 13 - 18 August 2006, abstract CDB0497.
8. Zimbabwe Human Development Report 2003, Poverty Reduction Forum, Institute of Development Studies, University of Zimbabwe. http://hdr.undp.org/en/reports/nationalreports/africa/zimbabwe/zimbabwe_2003_en.pdf (accessed 25 November 2007).
9. Addendum to 2006 Who Guidelines On Antiretroviral Therapy for HIV Infection in Adults and Adolescents: New Dosage Recommendations for Stavudine (D4T). http://www.who.int/hiv/art/ARTadultsaddendum.pdf (accessed 20 March 2008).
10. Division of Aids Table for Grading the Severity of Adult and Pediatric Adverse Events. Published December 2004. www.aactg.org/textmenu//science_sciguidelines.asp
11. Manosuthi W, Chimsuntorn S, Likanonsakul S, Sungkanuparph S. Safety and efficacy of a generic fixed-dose combination of stavudine, lamivudine and nevirapine antiretroviral therapy between HIV-infected patients with baseline CD4 <50 versus CD4 > or = 50 cells/mm3. *AIDS Res Ther* 2007; 4: 6.
12. Pensi T. Fixed dose combination of lamivudine, stavudine and nevirapine in the treatment of pediatric HIV infection: a preliminary report. *Indian Pediatr* 2007; 44: 519-521.
13. Mosam A, Cassol E, Page T, *et al.* Generic antiretroviral efficacy in AIDS-associated Kaposi's sarcoma in sub-Saharan Africa. *AIDS* 2005; 19: 441-443.
14. Marazzi MC, Germano P, Liotta G, *et al.* Safety of nevirapine-containing antiretroviral triple therapy regimens to prevent vertical transmission in an African cohort of HIV-1-infected pregnant women. *HIV Med* 2006; 7: 338-344.
15. Mosam A, Coovadia H, Sharon C, *et al.* Generic HAART in South Africa. Efficacy of fixed dose nevirapine, stavudine and lamivudine. XVI International AIDS Conference, Toronto, Canada, 13 - 18 August 2006, abstract CDB0598.
16. Manosuthi W, Chaovavanich A, Prasithsirikul W, *et al.* Efficacy and metabolic complications after 96 weeks of a generic fixed-dose combination of stavudine, lamivudine and nevirapine among advanced HIV-infected patients. IAS Conference, 22-25 July, Sydney, Australia, abstract WEPEB057.
17. Sungkanuparph S, Manosuthi W, Kiertiburanakul S, Chantratitra W. Tenofovir resistance among HIV-infected patients failing a fixed-dose combination of stavudine, lamivudine, and nevirapine in a resource-limited setting. *AIDS Patient Care STDS* 2007; 21: 711-714.
18. Laurent C, Kouanfack C, Koulla-Shiro S, *et al.* Long-term safety, effectiveness and quality of a generic fixed-dose combination of nevirapine, stavudine and lamivudine. *AIDS* 2007; 21: 768-771.
19. Calmy A, Pinoges L, Szumilin E, *et al.* Generic fixed-dose combination antiretroviral treatment in resource-poor settings: multicentric observational cohort. *AIDS* 2006; 20: 1163-1169.
20. Pujari SN, Patel AK, Naik E, *et al.* Effectiveness of generic fixed-dose combinations of highly active antiretroviral therapy for treatment of HIV infection in India. *J Acquir Immune Defic Syndr* 2004; 15: 1566-1569.

CASE STUDY

DEVELOPMENT AND IMPLEMENTATION OF AN HIV/AIDS TRIALS MANAGEMENT SYSTEM: A GEOGRAPHICAL INFORMATION SYSTEMS APPROACH

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Introduction. Researchers, practitioners and policymakers make decisions at all levels – from local to international. Accessible, integrated and up-to-date evidence is essential for successful and responsive decision-making. A current trials register of randomised and clinically controlled trials of HIV/AIDS interventions can provide invaluable information to decision-making processes. Using the newly emerging geographical information systems (GIS) technology, we have developed a tool which assists such decisions.

Objective. To demonstrate how the tool provides consistent, quantitative information in an accessible format, making it a key tool in evidence-based decision-making.
Methods. We identified all HIV/AIDS trials in relation to publications for the period 1980 - 2007, using both electronic and manual search methods. To facilitate searching the trials register, studies were coded by using a comprehensive but user-friendly coding sheet. We captured the geographical co-ordinates for each trial and used the ArcGIS 9 mapping software to design and develop a geodatabase of trials.

Results. The geodatabase delivered the complete requirements for a data-driven information system, featuring the following functions: (*i*) a clear display of the spatial distribution of HIV/AIDS trials around the world; (*ii*) identification of and access to information about any particular trial on a map; and (*iii*) a global resource of potential information on the safety and efficacy of prevention and treatment measures.

Conclusions. The building of a functioning HIV/AIDS trials management system can provide policymakers, researchers and practitioners with accessible, integrated and up-to-date evidence that is essential to successful and dynamic decision-making.

In 2005, the World Health Organization (WHO) launched the International Clinical Trials Registry Platform (ICTRP) project to set international norms and standards for clinical trial registration and reporting. Registering trials at inception in an international registry and making them publicly accessible offers many benefits, including: (*i*) guarding against the threat of suppressing negative findings and exaggerating positive ones;[1] (*ii*) preventing duplication of effort by improving transparency;[2,3] (*iii*) avoiding misleading conclusions being drawn from forms of care that are most likely to benefit patients;[4] and (*iv*) identifying research gaps that should be addressed in future trials. Registries of clinical trials also provide an important mechanism by which members of the public can learn of ongoing and completed trials and that may positively influence their participation in such trials as an opportunity to contribute to research.[5]

In support of a comprehensive approach to public registration and reporting of clinical trials, the International Committee of Medical Journal Editors (ICMJE) stipulated that all trials commencing enrolment after 1 July 2005 would be published in ICMJE member journals only if they had been registered with an appropriate repository.[5] A number of publicly accessible registries of clinical trials are currently available to meet various specific needs,[6] the two major ones being ClinicalTrials.gov, run by the USA's National Library of Medicine, and the metaRegister of Controlled Trials (mRCT), established by Current Controlled Trials.[7] ClinicalTrials.gov provides information

about registered trials including: a summary of the purpose of the study; eligibility criteria; trial location; study design; trial phase; disease or condition; and drug or therapy under study. Trials registered on the mRCT receive a unique number (the International Standard Randomized Controlled Trial Number (ISRCTN)), which helps to eliminate double registering and allows a trial to be tracked and identified throughout its life cycle.[8] In addition to the ISRCTN, mRCT lists the following information about each trial: title; sponsor; disease or condition under study; hypothesis and objectives; eligibility; current status; and contact information.[5]

In this paper, we present the methods employed by the Cochrane HIV/AIDS Review Group (CRG) in developing an HIV/AIDS trials management system (HTMS), coupling GIS technology and a relational database management system to locate HIV/AIDS randomised clinical trials (RCTs) and controlled clinical trials (CCTs) throughout the world.

A GIS is a system of computer software and hardware, data and personnel that makes it possible to enter, manipulate, analyse, and present spatially referenced information, i.e. information tied to a locus on the earth's surface.[9] Several authors have described the applications of GIS in the area of public health.[10-14] In the past decade, however, the scope of GIS and health policy and practice has risen to prominence, and researchers, practitioners and policymakers are recognising that the GIS tool can facilitate efficient and effective decision-making. This paper presents the features of the HTMS and demonstrates, with an example of the application, how the system can support decisionmakers.

METHODS

IDENTIFICATION OF TRIALS

The HTMS consists of two components: the first involves the identification of HIV/AIDS trials from electronic bibliographic database sources which include PubMed/MEDLINE, EMBASE, and AIDSearch, as well as from 'hand searching' non-indexed journals and conference proceedings. The included studies are all RCTs and CCTs evaluating the efficacy or effectiveness of preventing or treating HIV/AIDS and related conditions. Trials which assess interventions that may have an effect on HIV transmission (e.g. condom use) are included, but those trials assessing interventions specific to other sexually transmitted infections are excluded, as are trials which only assess safety (so-called phase I trials).

All identified trials are imported into a study-based register in MeerKat, an in-house bibliographic management software package built in Microsoft Access and developed by the international organisation, the Cochrane Collaboration (CC).[15] Owing to the relational nature of the database, different fields can be related to each other, allowing references, studies, reviews and authors to be interlinked. To facilitate searching in the trials register, the studies are coded, using a comprehensive and user-friendly coding sheet. Table I lists the required data elements for the coding sheet.

The study name is a unique text assigned to each trial, and is usually the last name of the first author followed by the publication year, e.g. Brown 2006. For any subsequent publications by the same author in the same year, the trial is assigned the study name Brown1 2006, Brown2 2006, etc. The status of the study gives an indication of whether the trial is closed, ongoing, planned or was stopped early. Study design types include RCT, CCT or systematic review (a study type which compiles and pools the data of RCT results of a particular intervention). The register status reveals whether a particular trial is pending, accepted or rejected. Other data elements such as intervention, outcomes and the ISRCTN are also captured. Free fields are available to capture additional information when specific elements of trials are being studied, such as aspects of the methodological quality.

TABLE I. DATA ELEMENTS FOR THE CODING SHEET

Study			
Study name			
Status of study			
Closed	Open/Ongoing	Planned	Stopped early
Design			
RCT	CCT	Systematic review	
Register status			
Pending	Accepted	Rejected	
Intervention			
Treatment	Prevention		
Outcomes			
Morbidity	Mortality/Survival	Transmission (MTCT)	
Geographical co-ordinates			
Latitude	Longitude		
ISRCTN			

To facilitate the mapping process, we capture the location of the trial in terms of latitude and longitude. For multi-centre trials, the geographical co-ordinates of each centre are recorded. The coding sheet mirrors the user-friendly input screens of the register (Fig. 1). Fields contain drop-down lists from which items have to be selected, to avoid typing errors.

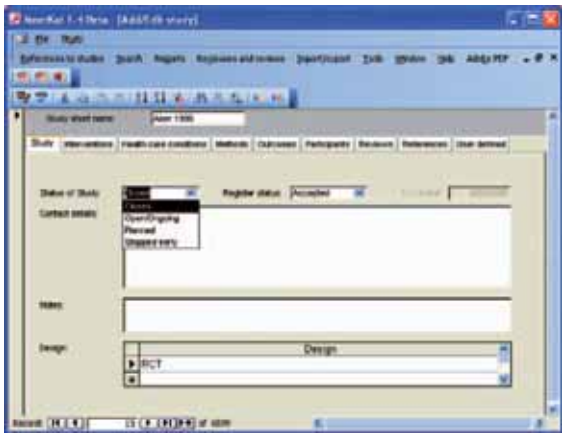

Fig. 1. Input screen of the register.

INTEGRATION OF THE REGISTER INTO GIS

The second component involves implementing the GIS platform of the HTMS. Using the Environmental Systems Research Institute family of software known as ArcGIS 9, we created a new geodatabase in ArcCatalog, which involved integrating the trials register in MeerKat (Microsoft Access) with a series of GIS map layers. The datasets included continents and countries' boundaries. The longitude and latitude of each study identifies the X and Y spatial co-ordinates in geographical space. This allowed us to map the geographical location of each study.

RESULTS

To date, the database contains 7 382 records relating to publications in the years 1980 - 2007, and is being updated quarterly, continually coded and regularly quality-controlled by random checks of the data. The architecture of the HTMS is shown in Fig. 2.[16]

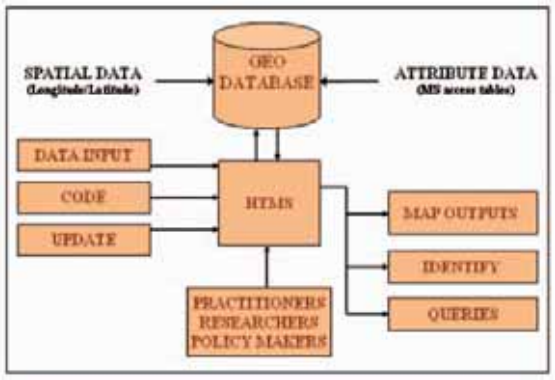

Fig. 2. Architecture of the HTMS.

SPATIAL DISTRIBUTION OF TRIALS

The spatial distribution of HIV/AIDS trials across the world is clearly displayed. For example, spatially distributing a convenience sample of 53 trials from the year 2003 showed that 50 of these were RCTs and 3 were CCTs (Fig. 3). Further analysis carried out by compiling a report (Fig. 4) or chart (Fig. 5) indicated the number of trials conducted on each continent.

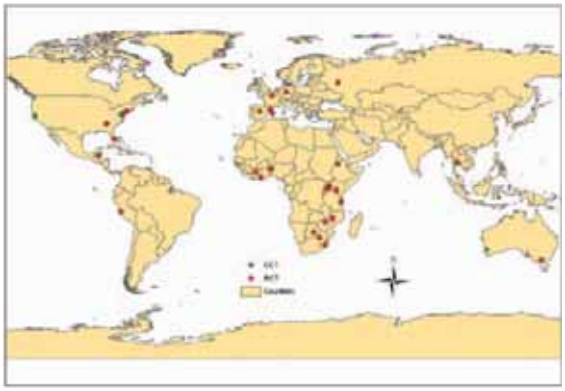

Fig. 3. Spatial distribution of 50 RCTs and 3 CCTs from the year 2003.

CONTINENT	NoOfTrial
Asia	1
North America	22
Europe	6
Africa	20
South America	2
Oceania	0
Australia	2
Antarctica	0

Fig. 4. Report output.

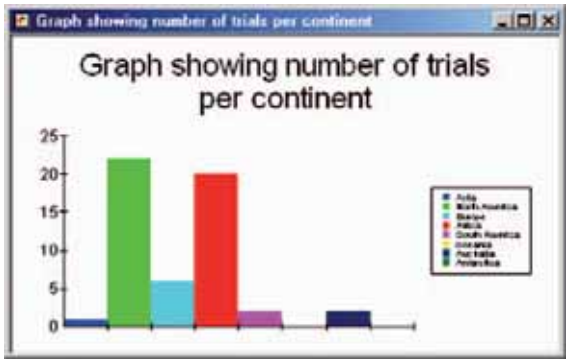

Fig. 5. Graph output.

IDENTIFICATION OF TRIALS

The system provides a foundation and suite of tools for monitoring and tracking ongoing, completed and published trials and their characteristics. When the user clicks on a particular trial, the resulting window displays all attributes of the trial, as shown in Fig. 6.

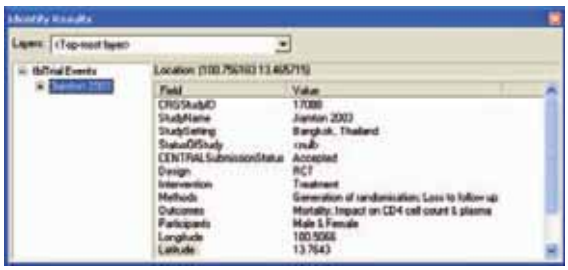

Fig. 6. Table of attributes.

QUERYING THE HTMS

The **Find** button facilitates searching the HTMS. Because the trials are coded in different ways, as shown in Table I, locating treatment trials can be done by typing 'treatment' in the **Find** search box, selecting 'tbltrials' from the **In** drop-down menu list, selecting 'intervention' from the **In fields** drop-down menu list, and finally clicking on Find. The **Find** dialogue box will then list all intervention trials, as shown in Fig. 7, and, on double-clicking, that selected will be highlighted on the active map.

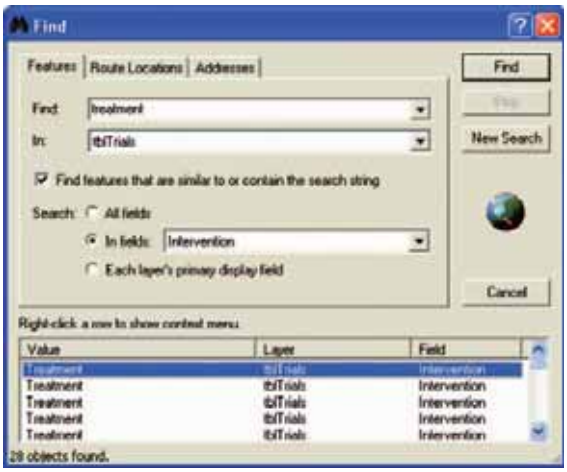

Fig. 7. Querying the HTMS.

DISCUSSION AND CONCLUSION

The need for comprehensive, up-to-date and easily accessible trials registers has been recognised for years. In the last two years, we have designed and implemented a system which offers an infrastructure of support to researchers, practitioners and policymakers, with up-to- date and reliable trials that satisfies the right of all children and adults to have access to all the available evidence regarding HIV/AIDS trials. The geodatabase developed in this work is a comprehensive source of clinical information obtained by searching electronic bibliographic sources as well as hand searching non-indexed journals and conference proceedings. The compilation of the HTMS serves the purpose of continual identification and data warehousing of HIV/AIDS trials across the world.

In addition, the HTMS is a landmark initiative in tracking and monitoring HIV/AIDS RCTs and CCTs in global health research endeavours. Instead of depending solely on information in text format, the visual synthesis of information into a picture and the overlay of quantitative graphics allow users of the system to realise the spatial distribution of the trials across the world in a clear manner. The system presented here can be used for trials characterisation and also serve as a valuable source of information for researchers as they initiate and design their studies. Another strength of the system is its ability to act as a research tool for analysing trends in the conduct of trials around the globe. For example, since sub-Saharan Africa carries the heaviest burden of the HIV/AIDS pandemic, researchers can follow in a timely and detailed way the location of trials conducted in this region, which can provide both an historical tracking system as well as identifying gaps where HIV/AIDS prevalence is high but clinical intervention research is lacking.

As much as the HTMS has several success factors, it also has its share of limitations. The HTMS is only as good as the data it contains; it is currently being updated and maintained by a single person, with support from a number of trial coders. Populating the HTMS is a labour-intensive process and entails a conscientious effort which includes downloading records from electronic bibliographic sources, followed by the necessary formatting, configuration and de-duplication of records prior to importing them into the register. The challenge is to continually monitor and improve the quality of the records and ensure that they are coded in the correct coding categories as shown in Table I. The currency of the information in the trials bank is of great importance, and the accuracy and completeness of the data are critical so that the maps communicate effectively and inform the broad range of users who may view them without misinformation.

The register put together by ClinicalTrials.gov (http://www.clinicaltrials.gov/ct/action/GetStudy) also offers a geographical perspective of clinical trials and allows website visitors to click on a region to display studies with locations in that region. However, ClinicalTrials.gov lists trials that are currently under way, meaning that the register is a prospective one whilst the HTMS is retrospective and contains all HIV/AIDS RCTs and CCTs since 1980, including the human T-lymphotropic virus type III (HTLV III) trials, as HIV was commonly referred to before 1985. The African Clinical Trials Portal (http://www.africaclinicaltrials.org/) is yet another comprehensive online resource for easily accessible information on malaria, HIV/AIDS and TB clinical trials in Africa. The portal is a one-stop resource that allows users to access clinical trial information using a database of pre-licensure clinical trials of malaria, HIV/AIDS and TB drugs, vaccines and microbicides that are currently under way in Africa.

Similarly to ClinicalTrials.gov, the African Clinical Trials Portal is a prospective register where data manipulation

at the user end is restricted. To our knowledge, the HTMS is the first retrospective compilation of HIV/AIDS trials around the world. As the information technology revolution (including online systems), the World Wide Web, and other electronic information systems continue to expand both the volume and accessibility of information,[17] the next component of this project will involve translating the desktop HTMS into a web-based HTMS to publicly make available all the clinical trials information. Within the web-based system, multiple users from different locations will only require their existing web browser to view geographical data and access the trials-related data, without the requirements or costs of installing GIS software packages.

With the implementation of the international HTMS, the need to communicate HIV/AIDS trials-related data to researchers, practitioners and policymakers has begun to be achieved as it proves to be an effective information-gathering and management tool. Our plans to make the data available online will increase the accessibility of the information. Ultimately, we hope that policymakers and researchers will find the HTMS a transparent means of capturing trial information so that all trial results are available to all parties involved – including consumers and their carers. In the future, the use of GIS technology could be regarded as a means of facilitating access to evidence-based health care data and contributing to policy development.

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REFERENCES

1. Abbasi K. Compulsory registration of clinical trials. *BMJ* 2004; 329: 637-638.
2. Tonks A. Registering clinical trials. *BMJ* 1999; 319: 1565-1568.
3. Krleza-Jeric K, Chan A, Dickersin K, Sim I, Grimshaw J, Gluud C. Principles for international registration and results from human trials of health related interventions: Ottawa statement (part 1). *BMJ* 2005; 330: 956-958.
4. Faure H. In Mayor S. New register will track trials funded by the NHS. *BMJ* 2003; 327: 1010.
5. Gold JL, Studdert DM. Clinical trials registries: a reform that is past due. *J Law MedEthics* 2005; 33(4): 811-820.
6. Krleza-Jeric K. Clincial trialr: the differing views of industry, the WHO and the Ottawa Group. *PloS Med* 2005; 2(11): e378.
7. Dickersin K, Rennie D. Registering clinical trials. *JAMA* 2003; 290: 516-523.
8. WHO: International Clinical Trials Registry Platform. Geneva: World Health Organization. http://www.who.int/ictrp/en (accessed 18 May 2006).
9. Geographic Information Systems Learning Laboratory: What is GIS? http://webpub.allegheny.edu/dept/envisci/GISLab/whatisgis01b.htm (accessed 10 June 2005).
10. Moore DA, Carpenter TE. Spatial analytical methods and geographic information systems: Use in health research and epidemiology. *Epidemiol Rev* 1999; 21(2), 143-161.
11. Jerrett M, Burnett R, Golberg M, *et al.* Spatial analysis for environmental health research concepts, methods, and examples. *J Toxicol Environ Health Part A* 2003; 66: 1783-1810.
12. Selvin S, Merrill DW, Erdmann C, White M, Ragland K. Breast cancer detection: maps of 2 San Francisco bay area counties. *Am J Public Health* 1998; 88: 1186-1192.
13. Shuai J, Buck P, Sockett P, Aramini J, Pollari F. A GIS-driven integrated real-time surveillance pilot system for national West Nile virus dead bird surveillance in Canada. *Int J Health Geographics* 2006; 5: 17.
14. Richards TB, Croner CM. Geographic information systems and public health: mapping the future. *Public Health Reports* 1999; 114(4): 359-361.
15. MeerKat. http://www.cc-ims.net/Projects/MeerKat/ (accessed 13 October 2006).
16. Busgeeth K, Rivett U. The use of a spatial information system in the management of South Africa. *Int J Health Geographics* 2004; 3: 13.
17. Riner ME, Cunningham C, Johnson A. Public health education and practice using geographic information system technology. *Public Health Nurs* 2004; 21(1): 57-65.