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FROM THE EDITOR

The editorial staff of the *Southern African Journal of HIV Medicine* would like to take this opportunity to congratulate Dr Francois Venter on his election as President of the Southern African HIV Clinicians Society. I am sure that under Francois' vigorous leadership the Society will continue to expand and become even more significant in the field of HIV medicine on our continent. Francois is an experienced clinician in the field and is currently working in the public sector. He thus provides a bridge between the public sector and the private sector and would be an important catalyst in developing and promoting public-private sector partnerships.

This issue of the journal provides clinicians with two important guidelines in the field of antiretroviral (ARV) therapies, namely the issue of nucleoside reverse transcriptase inhibitor (NRTI)-associated lactic acidosis and ARV drug resistance. Ironically the former is associated in most instances with our extremely adherent patients and the latter with our least adherent patients. Stavudine, which at the present time is included as a first-line drug in most regimens in the developing world, is included for very good reasons: it is effective, inexpensive and easy to take. Regrettably, however, it has been linked to a number of conditions associated with mitochondrial toxicities, lipoatrophy, peripheral neuropathy and lactic acidosis to name but a few. The time has come when this drug needs to be replaced in regimens in the developing world. We eagerly await the registration of tenofovir in South Africa, which will go a long way towards alleviating the distressing side-effects of stavudine. Until this happens clinicians need to have a heightened awareness of lactic acidosis and institute appropriate laboratory monitoring and prompt management in order to avoid the not insignificant morbidity and mortality associated with the condition.

Resistance of HIV to ARV therapies is an issue in both the developed and developing world. The difference between these situations, however, is that in the developed world there are many more options with regard to both testing and sequencing of therapy. In the developing world, where options for drug therapies are limited, the clinicians' guide published in this issue will provide immeasurable support for the treating doctor.

DES MARTIN
Editor

MESSAGE FROM THE EXECUTIVE

On behalf of the newly elected executive, I would like to extend my thanks to the 10 500 members of the Southern African HIV Clinicians Society for all your support. We are going to need it, as the challenges posed by the epidemic appear to be getting greater with each passing year. As part of an overall review, the new executive will be taking an intensive look at our activities in the light of expanded access to care across the southern African region. New branches are cropping up across the region, and a major role for the society is maintaining our massive database so that, no matter where our members are, effective communication is possible to ensure that those on the ground have the information they need to do the best job possible.

In terms of immediate activities, we will be revamping the *Journal* and *Transcript*, our major method of communication. The previous president, Professor Des Martin, will remain as the *Journal's* editor and Ms Penny Penhall will continue editing *Transcript*, with more scope to stimulate debate and controversy! The website will also be changing, and will be freely accessible to all in future, led by Dr Steve Andrews.

Professor Gary Maartens will be co-ordinating the Colleges of Medicine's highly successful HIV Management Diploma, and the Society will be encouraging as many of you to write it as possible.

The Society's extremely successful collaboration with the Foundation for Professional Development is set to continue – thousands of health care workers have been trained through their courses, and the Society will continue to ensure the quality of this course and its relevance to the southern African context. Dr David Spencer will be leading the Society's advocacy wing, strengthening our ties with civil society. Other responsibilities will be allocated as needed.

I welcome any suggestions going forward, and will be calling on members to assist us where possible. Finally, much thanks to the previous executive, as well as Penny Penhall, the Society's manager, Pat Solan, responsible for the database, and Jean Solan, who manages our finances, for making this one of the biggest medical organisations in the world.

I look forward to meeting many of you through branch meetings and events and I hope we are able to do great things in 2006.

FRANCOIS VENTER
President

TRIALS AND TRIBULATIONS

The medical maxim of 'First do no harm' is never more relevant than during development of a medicinal agent or intervention, whether it be drug, vaccine, diagnostic or procedure. Over many years a phased clinical trial process has been developed along with safety and monitoring processes to ensure human subject dignity, privacy and autonomy, and the minimisation of risk as well as research integrity.

Before any testing in human subjects the process involves pre-clinical work, including toxicity studies, wherever possible in animal models. Human subject testing then follows with phase 1 trials, often in small numbers (10 - 100) of adult volunteers who may or may not have the condition under consideration, and under very carefully monitored trial conditions. This phase tests safety only. Phase 2 is conducted in slightly larger groups (100s) of individuals (now possibly involving the target population), again mostly testing safety, but also ideal dose and possibly some indicators of activity. In Phase 3, the well-known efficacy studies, much larger groups (100s - 1 000s) of the target population are included and while safety should still be carefully monitored the main question is efficacy. Efficacy can be tested most rigorously if a comparison group is included, usually receiving the 'standard of care' in order to allow the trial to be performed adequately and without unfair disadvantage to the experimental group.

Every phase of the process requires careful review by independent regulatory and ethical groups to ensure that all considerations of safety and indicators to move forward are met. In dose escalation studies, safety pauses should again be incorporated. Where possible independent safety monitoring groups should have access to trial data to ensure that safety is reviewed objectively and studies modified or stopped for reasons of safety and/or efficacy.

This process is incorporated within the concept of 'Good Clinical Practice', and I would contend that somehow GCP has got lost in the minutiae of whether our case report forms are filled out perfectly in black or blue ink. While detail is important and an important element of clinical research, the primary purpose of GCP is to meet the highest levels of human subject protection while conducting well-designed clinical trials that inform the developmental process.

Two events in the last week have highlighted these issues. First is the recent disaster at Northwick Park Hospital, London. Six healthy young men – including British Asians, an Australian, a New Zealander, and a South African, contracted by the US drug testing company Parexel to test the anti-cancer drug TGN1412 – went into sudden multiple organ failure as a result of unexpected massive inflammatory reactions. Why did the rigorous rules laid down by the Medicines and Healthcare Products Regulatory Agency (MHRA) fail to halt these dreadful events? The MHRA has begun an investigation into the calamity, which should provide answers to these questions. It may be months before any inquiries give answers, and in the meantime these previously healthy volunteers are fighting for their lives.

There are three reported questionable aspects to this disaster:

1. The drug is a monoclonal antibody that targets the CD28 site on the surfaces of T cells, kick-starting the body's immune system into action. One could argue for a trial design for early phase 1 studies to be conducted not in healthy volunteers whose immune systems are normal and vigorous but in cancer patients or individuals with autoimmune disorders. Because the monoclonal is humanised it is not always easy to interpret animal toxicity data. Finally, new technology involving micro-dosing where local systems are set up in blisters on the skin may give more information in trials of this kind before proceeding to normal dosing.
2. Secondly, the dose escalation in this study was reportedly performed inordinately rapidly and, some would argue, without sufficient safety pause.
3. Finally, the study participant recompensation for the trial was apparently in the order of £2 000 each, and it has been argued that inducements of this magnitude may cloud volunteers' ability to judge personal risk and lead to non-disclosure of pre-existing medical conditions, etc.

The next item of news is local: weekend papers ran a story on senior members of government who have supported use of unproven traditional medicines for AIDS, and this at the expense of clinically tried and tested licensed antiretroviral agents.

Ubhejane is the secret recipe of Zeblon Gwala, a former truck driver from KZN who claims that its ingredients came to him in a dream from his healer grandfather. Apparently he personally collects the 89 herbal ingredients from all over South Africa and mixes them manually. It is then sold in unlabelled 2-litre plastic bottles for R342 each and lasts 2 weeks. More seriously, aside from any possible toxicity, patients commencing use of Ubhejane are reportedly encouraged to stop or not use prescribed antiretrovirals.

The *Sunday Times* reported that KZN Minister of Health, the eThekwini Mayor and the special advisor to the KZN Premier have openly encouraged people to take this product despite no evidence of conventional clinical testing for either safety or efficacy. If this is true it is both dangerous and unethical, particularly if it is recommended as a substitute for a proven life-saving treatment.

Mr Gwala claims that he has records of all patients on this treatment, but could not supply details to the *Sunday Times*. Gwala is quoted as saying: 'I do keep files but there are so many and I don't know which has these things in it'.

With 5 - 6 million South Africans infected with HIV we would be ecstatic if Ubhejane or some other indigenous medicine could be found to be part of the armamentarium against HIV, but in order to prove any new product's worth and safety, and before wild claims of efficacy are made to a desperate public, we need to follow drug testing protocols developed to protect the public.

LINDA-GAIL BEKKER
Managing Editor

GUIDELINES FOR THE PREVENTION, DIAGNOSIS AND MANAGEMENT OF NRTI-ASSOCIATED SYMPTOMATIC HYPERLACTATAEMIA AND LACTIC ACIDOSIS

Southern African HIV Clinicians Society

Expanding access to antiretrovirals (ARVs) in southern Africa has dramatically impacted on the lives of those HIV-infected people who are able to obtain these drugs. Highly active antiretroviral therapy (HAART) has been shown to significantly reduce HIV-related morbidity and mortality in developed and developing world settings.[1,2] However, ARVs, like most pharmaceutical agents, can result in side-effects and toxicities that in some instances may be life-threatening, especially if there is delay in their recognition.

One of the most challenging and dangerous side-effects is symptomatic hyperlactataemia that may evolve to lactic acidosis, a toxicity that may result from treatment with the nucleoside reverse transcriptase inhibitors (NRTIs). The first cases were described in the late 1980s, with fatalities being described in 1993.

PATHOPHYSIOLOGY

Lactate is normally produced by all the body's cells, as part of anaerobic metabolism. Certain cells (such as erythrocytes) lack mitochondria for aerobic respiration and are obligate lactate producers, while other cells will switch to predominant lactate production if the aerobic cycle is compromised, because of either a lack of available cellular oxygen or compromised mitochondrial oxidative phosphorylation. The liver is a key organ for the removal of lactate from the circulation, along with the kidneys. The steady state of lactate production and removal is usually only compromised when there is significant over-production *and* compromised liver function. Impairment of renal function seems to increase the risk.

NRTIs suppress HIV replication by inhibiting the viral enzyme reverse transcriptase. However, this class of drugs also has the potential to directly inhibit the human enzyme mitochondrial DNA polymerase gamma (γ), which is responsible for mitochondrial DNA synthesis. Reduced DNA synthesis results in less synthesis of essential mitochondrial proteins. The consequence is the formation of mitochondria which are structurally and functionally impaired, resulting in decreased oxidative capacity of each mitochondrium. Lactate over-production and cellular dysfunction result.

Important: The management of this condition is complex and these guidelines are based on expert experience rather than prospective clinical trials. Clinical common sense is advised in all cases. Guidelines may change as better evidence becomes available.

Different NRTIs have different risk profiles for causing hyperlactataemia. Their risk is directly proportional to their inhibitory effect on polymerase γ, in the following order (highest to lowest risk):

1. Combination of didanosine (ddI) and stavudine (d4T)
2. ddI
3. d4T
4. Zidovudine (AZT)
5. Lamivudine (3TC), abacavir (ABC) and the nucleotide reverse transcriptase inhibitor, tenofovir (TDF). These drugs are usually only implicated if used in combination with higher-risk drugs.

Other manifestations of NRTI mitochondrial toxicity are hepatic steatosis, peripheral neuropathy, lipoatrophy, pancreatitis, myopathy, cardiomyopathy, HIV-associated neuromuscular weakness syndrome (a Guillain-Barré-like syndrome that occurs secondary to NRTIs[3]) and cytopenias.

DEFINITIONS

A normal venous lactate level is less than 2.5 mmol/l and arterial lactate less than 2.0 mmol/l.

Hyperlactataemia is present when lactate is raised but blood pH is > 7.35 and standard bicarbonate > 20 mmol/l, and may be asymptomatic or symptomatic. Asymptomatic hyperlactataemia is common in patients on NRTIs (occurs in up to 25% of patients), but does not predict for the symptomatic form of the disease. It represents a state of physiological compensation. Symptomatic hyperlactataemia carries a good prognosis if recognised early and if there is no liver dysfunction.

Lactic acidosis is diagnosed when pH < 7.35 and/or standard bicarbonate < 20 together with raised lactate. The lactate level in this setting is typically > 5. Reaching this stage means that significant failure of the physiological compensating mechanisms is present, and this carries a much worse prognosis. In lactic acidosis the pH may be in the normal range (due to respiratory compensation) but the standard bicarbonate is always < 20. There is invariably multiple organ dysfunction, especially hepatic.

Symptomatic hyperlactataemia occurs in 0.4 - 9% of patients on NRTI therapy, whereas lactic acidosis occurs in 0.1 - 0.4%.[4]

RISK FACTORS

The following have been identified as risk factors:

- High body mass index (BMI) – evidence from one of the South African cohorts suggests that rapid weight gain is also a risk factor.
- Gender – women are at greater risk.
- Pregnancy – a high risk of lactic acidosis has been noted in pregnancy when the ddI and d4T combination has been used.
- Underlying liver disease – this may impair lactate clearance.
- Age – symptomatic hyperlactataemia/lactic acidosis appears to be unusual in younger children, as are the other manifestations of mitochondrial toxicity, although cases have been reported in South Africa.

It is unclear whether co-administration with metformin is a risk factor. Metformin can also cause lactic acidosis in patients with organ dysfunction. However, it is a key drug in the treatment of diabetes, and its co-administration with NRTIs that have a high potential for hyperlactatemia (i.e. ddI, d4T) needs to be considered carefully, weighing the risks and benefits in the individual patient.

DIAGNOSIS

Apply the rule: if you consider the diagnosis, do the laboratory investigation immediately. Delays in diagnosis may be life-threatening.

Many conditions (Table I) may result in raised lactic acid and acidosis. Hyperlactataemia/lactic acidosis secondary to NRTIs is therefore a diagnosis of *exclusion.*

Symptoms may be very nonspecific and vague, and have generally been present and getting worse for weeks and occasionally months.

Key symptoms and signs include:

- Unintentional loss of weight (LOW) (especially > 5%).
- Gastrointestinal (GIT) symptoms, including nausea, vomiting, loss of appetite, abdominal pain and hepatomegaly.
- Weakness and fatigue.
- Dyspnoea, tachypnoea without respiratory cause.
- Unexplained tachycardia.

TABLE I. CAUSES OF HYPERLACTATAEMIA/LACTIC ACIDOSIS OTHER THAN NRTIs

- Sepsis
- Severe anaemia
- Hepatic failure
- Renal failure
- Pancreatitis
- Severe cardiac failure
- Severe dehydration
- Thiamine deficiency
- Other drugs (e.g. INH overdose, metformin)

- Myalgia.
- Peripheral oedema.
- Peripheral neuropathy and lipoatrophy often herald the onset of symptomatic hyperlactataemia.

The diagnosis is often missed initially, with symptomatic therapy being prescribed for GIT complaints. It is essential to maintain a high index of suspicion.

Symptomatic hyperlactataemia/lactic acidosis usually occurs after patients have been on NRTIs for several months (median 9 months). Typically the patient has initially experienced resolution of HIV- and opportunistic infection-related symptoms, has gained weight in the months after starting HAART and is virologically suppressed, then experiences a deterioration with the onset of hyperlactataemia and its associated weight loss and symptoms. However, we have documented rare cases in our cohorts that have occurred after only 2 months. It is unusual for symptomatic hyperlactataemia/lactic acidosis to develop after 2 years on therapy, but we have seen exceptions to this.

Clinical assessment should include evaluation of respiratory rate, abdominal examination and assessment for peripheral neuropathy. Tachypnoea in the absence of a respiratory cause is suggestive of metabolic acidosis.

The diagnosis is made by measuring venous or arterial lactate. The blood sample should be taken without the use of a tourniquet in a sodium fluoride tube and should reach the laboratory within 20 minutes on ice. However, if the sample is centrifuged on site and serum separated the serum sample then has 24 hours to reach a central laboratory.

Point-of-care devices for lactate measurement are particularly useful for primary care and rural facilities where access to a laboratory that is able to measure lactate is difficult. These devices have been validated in ICU settings and reliably determine lactate levels within ± 1 mmol/l of the laboratory measurement.[5] However, they have not yet been validated in a busy clinic setting. It is important that the blood used for the measurement is taken by venepuncture without a tourniquet and is not a fingerprick sample – the latter method has been shown to falsely elevate the lactate level at sites using these devices.

When doing blood gas sampling it is important to expel all residual heparin from the syringe before taking the sample. Failure to do this will cause a false lowering of pH.

Liver function tests, creatinine kinase, lipase and lactate dehydrogenase may be elevated in association with the lactate, but these do not have the necessary sensitivity or

specificity to be used as reliable diagnostic tests. It is, however, important to check lipase and liver functions in all patients with confirmed symptomatic hyperlactataemia/lactic acidosis to assess for coexistent pancreatitis and steatohepatitis. Blood gas levels should also be checked in all patients with symptomatic hyperlactataemia to confirm or exclude metabolic acidosis.

Once NRTI-associated lactic acidosis is established, it represents a profound metabolic insult. When the NRTIs are removed, it takes weeks to months to resolve.

DIFFERENTIAL DIAGNOSIS

Other causes for LOW and abdominal pain may mimic or coexist with hyperlactataemia/lactic acidosis.

Other causes for LOW to consider:

- Opportunistic infections (ask about tuberculosis symptoms).
- Lipoatrophy.
- Chronic diarrhoea with malabsorption.
- Virological failure.
- Depression.
- Malignancy.
- Undiagnosed diabetes.
- Poor diet and poor social circumstances.
- Hyperthyroidism.

Other causes for abdominal pain/symptoms to consider:

- Pancreatitis (check lipase).
- Hepatitis/steatohepatitis (check ALT/alkaline phosphatase and assess for hepatomegaly).
- Opportunistic infections or immune reconstitution inflammatory syndrome (IRIS) (e.g. abdominal TB).
- GIT intolerance of medication, especially if on concomitant TB treatment. Hyperlactataemia is often incorrectly diagnosed as this. GI intolerance to drugs rarely develops after months of therapy.
- Unrelated causes (e.g. pregnancy, diabetic ketoacidosis, appendicitis, peptic ulcer disease, pelvic inflammatory disease, urinary tract infections, pneumonia).

Other causes of tachypnoea and tachycardia, with or without the above:

- Respiratory conditions.
- Cardiac conditions.
- Anaemia.
- Sepsis.
- Diabetic ketoacidosis.
- Hyperthyroidism.
- Hypoperfusion due to diarrhoea, vomiting or inadequate fluid intake.

CONFOUNDERS

There are several causes of lactic acidosis other than NRTIs that need to be considered before the diagnosis is made (see Table I).

HIV-infected patients frequently present with infective gastroenteritis with diarrhoea and vomiting. If severe this may result in profound dehydration with poor tissue perfusion and a raised lactate level. In this situation once the patient is resuscitated with fluids the lactate will normalise. If the lactic acidosis is incorrectly attributed to the NRTIs in this situation an inappropriate interruption and switch in therapy may result. This may compromise future HAART options.

Similarly, septicaemia and other bacterial infections (e.g. pneumonia) may result in lactic acidosis that will resolve with fluid resuscitation, appropriate antibiotics and other supportive therapies.

However, to complicate matters further opportunistic infections and bacterial sepsis may unmask mitochondrial toxicity and precipitate a presentation with hyperlactataemia/lactic acidosis. Even with adequate fluid resuscitation and appropriate treatment for their infection these patients have persistently raised lactate levels. The presence of an infection therefore does not exclude the fact that the lactic acidosis is contributed to by the NRTIs.

PREVENTION

Recognising the syndrome before the person becomes acidotic is the most effective prevention, and symptoms tend to occur long before severe laboratory abnormalities are present. The mortality and morbidity of the condition dramatically increases in the presence of acidosis. The mortality rate with lactic acidosis is 30 - 60%. A practical approach is to educate patients to report any loss of weight, abdominal pain or vomiting lasting more than a few days, excessive fatigue, lipoatrophy or peripheral neuropathy symptoms (see addendum – patient education poster, p. 15). Weights should be monitored at every clinic visit, and when they drop by > 5% the lactate level should be measured, even if no other symptoms are present. Any patient with a severe or rapidly progressive NRTI-induced neuropathy (typically due to d4T or ddI) should also have the lactate level measured.

There is evidence that reducing the dose of d4T is associated with less toxicity (including hyperlactataemia) and equal efficacy. Patients developing other d4T-induced side-effects (e.g. peripheral neuropathy) should have their dose reduced (e.g. from 40 mg bd to 30 mg bd for those weighing > 60 kg, and from 30 mg bd to 20 mg bd in those < 60 kg) or switched to AZT. Another preventive strategy is to start women with a BMI > 28 on NRTIs with a lower risk of hyperlactataemia (3TC, ABC or TDF – but in the South African public sector AZT rather than d4T in the first-line regimen) or to switch them to these NRTIs if they gain weight to a BMI > 28 on HAART. This is a particularly high-risk group.

It is prudent to avoid using ddI and d4T in the same HAART regimen as this combination carries the highest risk for mitochondrial toxicity. This combination should only be used if there are no other options available.

Routine lactate measurement in asymptomatic patients is not recommended, as the correlation with the development of

symptoms is poor. Up to 25% of patients on NRTIs have asymptomatic hyperlactataemia with mild elevations in lactate levels, but only a minority will develop symptoms. Elevated lactate levels in the absence of symptoms are not a good predictor of symptomatic hyperlactataemia.

MANAGEMENT

Once the diagnosis is confirmed (raised lactate and *exclusion* of other causes), the following guidelines are suggested. Different facilities will have different treatment and monitoring options.

Stop the regimen even before the diagnosis is biochemically confirmed if you have a high index of suspicion. Do not stop the NRTIs alone – stop the entire regimen. It is better to interrupt a regimen for a short period than to continue a toxic regimen in the presence of suspected lactic acidosis.

The treatment guidelines presented below are largely based on anecdotal experience with the condition, by local and international clinicians and other published guidelines.[4,6-8] There are no prospective studies on the treatment of hyperlactataemia/lactic acidosis, and caution and common sense is urged by the guideline authors in all cases. These guidelines are based on the experience in South Africa being that most cases of symptomatic hyperlactataemia/lactic acidosis are caused by d4T in first-line therapy. We strongly urge that you consult an experienced treater in all cases, especially if d4T is not the offending drug.

Mild hyperlactataemia and minimal symptoms (lactate 2.5 – 5 and no metabolic acidosis – standard bicarbonate > 20)

The NRTI regimen should be switched to agents that are less likely to cause lactic acidosis (3TC, ABC or TDF if available – in the South African public sector switch from d4T to AZT in the first-line regimen) and the lactate rechecked within 3 days and then weekly until normalised. If symptoms are severe or the lactate continues to rise, or symptoms get worse despite the switch, HAART should be stopped and an expert treater consulted regarding the decision as to which HAART to restart when the lactate level has normalised.

If the lactate cannot be monitored in the way described, treatment should be stopped and treatment restarted when the lactate level has normalised and symptoms have resolved, following the guidelines below.

Moderately severe hyperlactataemia/moderate metabolic acidosis (lactate 5 – 10 and/or standard bicarbonate 15 – 20)

These patients should stop HAART, be observed as an inpatient for 1 - 2 days, and given oral vitamins (vitamin B complex 2 tablets bd and thiamine 100 mg bd), be well hydrated (orally or IVI) and have sepsis/opportunistic infections excluded. The lactate level should be rechecked, and when it is falling the patient can be discharged for outpatient follow-up provided he or she is clinically stable. HAART should only be recommenced when lactate and bicarbonate have normalised (this may take months), and the decision regarding what regimen to restart should be discussed with an experienced treater.

The choice as to what to recommence is one of:

1. AZT, 3TC and non-nucleoside reverse transcriptase inhibitor (NNRTI) with lactate monitoring at 2 weeks, 4 weeks and then monthly for a further 2 months and at any time symptoms recur. This is not an option if the patient had metabolic acidosis (standard bicarbonate < 20). It is important to note that there is limited evidence for the safety of recommencing AZT in this setting.[6]
2. TDF/3TC/NNRTI or ABC/3TC/NNRTI with lactate monitoring as above.
3. NNRTI with Kaletra (Kaletra dose here is 4 capsules bd due to NNRTI induction of Kaletra metabolism). Lactate monitoring not required.
4. Dual-boosted PI regimen (e.g. Kaletra + saquinavir). Lactate monitoring not required. This option is preferable to (3) if NNRTI resistance is documented or strongly suspected, but the option is not available in many southern African public sector programmes.

This decision is based on the prior HAART history, clinical picture, lactate level, arterial blood gas, degree of steatohepatitis at presentation and ability to monitor lactate on recommencement.

Patients with more severe disease should be recommenced on (3) (or (2) or (4) if available in the private sector), whereas those with a milder syndrome could be recommenced on (1). If a metabolic acidosis was present (1) should not be recommenced. There is no risk of recurrence of hyperlactataemia with (3) or (4), whereas with (1) there is a risk that AZT may cause relapse of hyperlactataemia (although the risk is lower than with d4T). There is less of a risk of recurrence with (2) than with (1), as ABC, TDF and 3TC have been infrequently associated with hyperlactataemia and usually when used in combination with a drug that is more likely to cause mitochondrial toxicity.

Also, the decision as to when to restart HAART is a balance between the patient's nadir CD4, their current CD4 and the severity of the hyperlactataemia/lactic acidosis. Patients with low nadirs should not have HAART withheld for too long, as they run the risk of acquiring new opportunistic infections. If lactate levels are persistently elevated in a patient with a low nadir CD4 count, a regimen without a risk of occurrence (NNRTI/Kaletra or dual-boosted protease inhibitor (PI)) should be considered and can be commenced before lactate has normalised.

Patient education is critical. Patients with hyper-lactataemia/lactic acidosis being rechallenged with a safer NRTI should understand the need for regular follow-up. Patients who live far from the health care facility, have transport difficulties, are unreliable or have follow-up compromised in any way, should not have NRTIs reintroduced.

Severe hyperlactataemia (lactate > 10 without metabolic acidosis) or significant lactic acidosis (raised lactate regardless of level and significant metabolic acidosis – standard bicarbonate < 15)

These patients should preferably be managed in a high-care facility as follows:

- Stop HAART
- IVI thiamine 100 mg 12-hourly and B-complex vitamins 1 amp 12-hourly.
- IVI fluids.
- Blood culture/urine culture/septic search *and* broad-spectrum antibiotic (e.g. third-generation cephalosporin or co-amoxyclav). This is important because sepsis may mimic or precipitate NRTI-associated lactic acidosis.
- Consider IVI $NaHCO_3$ if profound acidosis (e.g. 150 ml of 8.5% sodium bicarbonate added to a vacolitre of 5% dextrose water and infused at 80 - 100 ml per hour).
- Consider ventilation if respiratory fatigue occurs.
- Dialysis, inotropes and other supportive measures as necessary.
- Coenzyme Q, L-carnitine and other mitochondrial co-factors are used by some when available, but have very limited evidence for efficacy.
- If pancreatitis is present patients should be kept nil per mouth.
- Monitor lactate, blood gas, lipase, ALT and alkaline phosphatase.

Some of these patients demonstrate a biphasic course with initial improvement and then deterioration, often when they develop a superimposed pancreatitis.

These patients should be recommenced on Kaletra (lopinavir/ritonavir) 4 capsules bd and NNRTI or a dual boosted PI regimen (options (3) and (4) above) when lactate has normalised (this may take months). Other regimens that could potentially be used in these patients with less severe presentations are TDF/3TC/NNRTI or ABC/3TC/NNRTI with lactate monitoring on rechallenge as described above (option (2) above).

COVERING THE 'NNRTI TAIL' WITH LOPINAVIR/RITONAVIR (KALETRA)

When a HAART regimen containing an NNRTI (nevirapine or efavirenz) is stopped the NNRTI persists in the plasma for 1 - 2 weeks because of the long half-life of these drugs, unlike the NRTI component. This 'NNRTI tail' means that there is effective monotherapy with the NNRTI after the HAART is stopped, which predisposes to the development of NNRTI resistance. Provided patients are not vomiting and do not have either significant steatohepatitis or pancreatitis, it is suggested that when an NNRTI-containing regimen is stopped because of hyperlactataemia or lactic acidosis, 7 days of Kaletra (lopinavir/ritonavir) 4 tablets bd are prescribed to cover the NNRTI tail, thereby preventing effective monotherapy and the risk of NNRTI resistance developing.

PAEDIATRIC HYPERLACTATAEMIA/LACTIC ACIDOSIS

Initially paediatric symptomatic hyperlactataemia/lactic acidosis was considered very rare, but several local cases have been reported. Experience with this group is very limited, but symptoms and signs similar to those in adults seem to be present, although the differential diagnosis may be different. Management is similar to that of adults in terms of cessation of treatment and supportive measures. However, specialist advice should be sought in all cases.

PROGNOSIS

Poor prognostic markers are high lactate level, severe acidosis and coexistent pancreatitis. Patients who require ventilation and/or dialysis appear to have an extremely poor prognosis.

SWITCHING TO AZT

When d4T is switched to AZT it is frequently forgotten that monitoring for AZT haematological toxicity is required. The full blood count and differential count should be checked at baseline, then at 1, 2, 3 and 6 months, then 6-monthly. Do not start AZT in patients with a haemoglobin concentration < 8 g/dl.

THE FUTURE

Broader availability of TDF and ABC may make hyperlactataemia/lactic acidosis less common in the future. Until then, the availability of hand-held lactate monitors makes on-site diagnosis and monitoring a reality in public sector clinics. Increased access to these devices is encouraged.

Contact number. If there are any queries contact the Medicines Information Centre HIV Hotline (South Africa) (021) 406-6782.

Acknowledgement. This article is based on the practical experience of a large number of southern African clinicians as well as published evidence.

Guideline committee. Convenor: Graeme Meintjes; Committee: Francois Venter, Francesca Conradie, June Fabian, Gary Maartens, Douglas Wilson.

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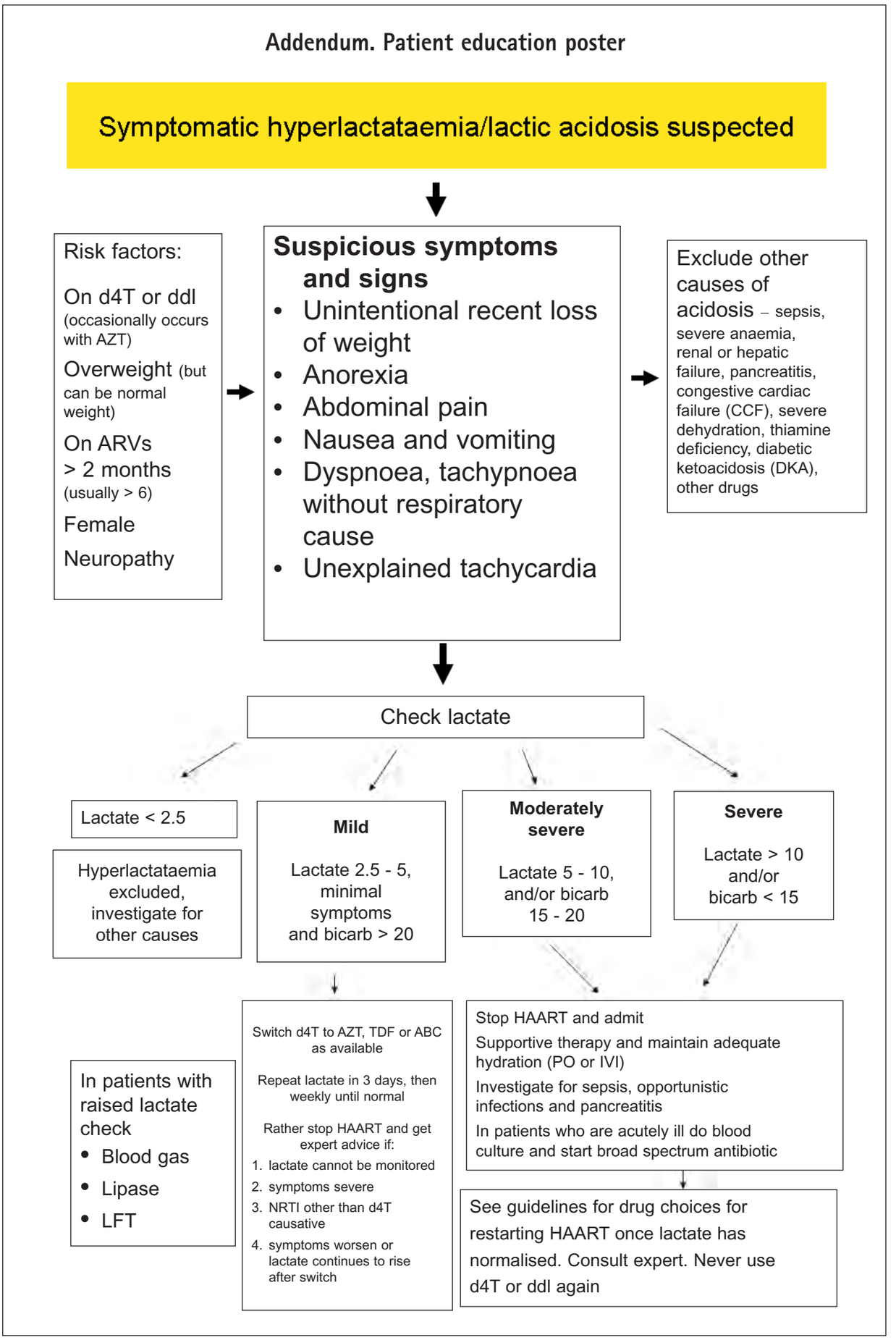
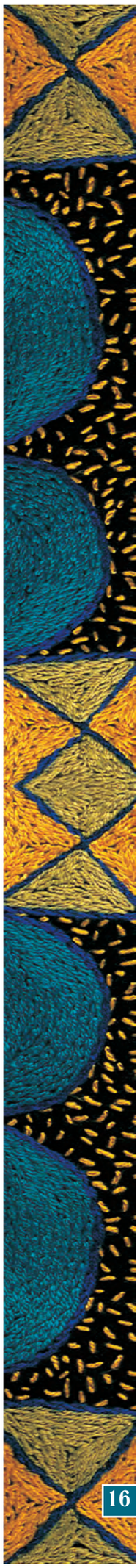
Addendum. Patient education poster





DEBATE

WHEN HIV CLINICIANS PREVENT SOCIAL SCIENTISTS FROM ACCESSING 'THEIR' PATIENTS: SOME ETHICAL CONCERNS

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There is an understandable tension between medical researchers and social scientists when it comes to AIDS-related research at clinic level. Clinics offering antiretroviral treatment exist primarily to assist patients – but many of them also provide 'data' for medical researchers. This may involve a randomised controlled trial, or simply the collection of data on adherence. A social scientist wishing to access patients to conduct interviews or focus groups thus (inevitably) appears to the HIV clinician as at best a disruption to an already over-stretched operation, and at worst a potentially confounding factor in his or her own research.

Given that the medical practitioner/researchers effectively control the clinics, the temptation to deny social scientists access to patients must be strong. As discussed below, this was the case with regard to two Cape Town clinics that prevented a clinical psychologist (working in my research unit) from conducting social science research. Although understandable, such unaccountable exercise of power denies patients the opportunity to participate in other research projects that may be of benefit to them (or society) in ways that HIV clinicians do not necessarily appreciate. As such, it violates the principle of informed consent. It is also problematic in that it restricts the AIDS research agenda to biomedical concerns. This is particularly worrying with regard to AIDS, where it is widely accepted (by social scientists and HIV clinicians alike) that social and psychological factors matter a great deal for HIV prevention and treatment interventions.

GATE-KEEPING BY MEDICAL RESEARCHER/PRACTITIONERS: A CASE STUDY

The wider Cape Town metropolitan area is home to several antiretroviral treatment and vaccine initiatives funded by NGOs and pharmaceutical companies. All of these entail collaboration with the Western Cape government (which has *de jure* ownership of the clinics). Most of the projects have strong links with university-based medical researchers, some of whom also offer medical or related support services to the projects. Many HIV clinicians are thus simultaneously medical practitioners and researchers.

In this world of overlap between service provision and research interests, patients on antiretroviral treatment are both beneficiaries and research subjects. They enter a world entirely controlled by medical practitioner/researchers. Although the clinics are technically under the control of the government, decision-making power in effect is ceded to the largely foreign-funded doctors and researchers who run the interventions. They decide who can be on the premises, what research is 'acceptable', and who can interview the patients. This gatekeeper role has serious implications for social scientists trying to conduct research – as one of my PhD students discovered to her cost.

The student, a trained and registered clinical psychologist, wanted to conduct research into the psychological well-being and coping strategies of low socio-economic status mothers on antiretroviral treatment. Her research entailed recruiting 75 HIV-positive mothers and interviewing them when they started treatment, and then again after 4, 12 and 24 weeks. A sample of 75 HIV-negative mothers from the community was to be recruited as the comparison group. The aim of the research was to explore the challenges to women's care-giving and psychological well-being posed by negotiating the multiple roles of living with HIV, caring for young children and dealing with the general stressors associated with poverty. She was particularly interested in drawing out the implications of these multiple roles for women's adherence to antiretroviral therapy.

In addition to interviewing the women, the student stated her intention to ask the participants for permission to access their medical files so that she could collect data on CD4 counts, viral loads, clinical staging and adherence information. She stressed that this information would only be collected at the convenience of the clinic. In her research protocol, she acknowledged that she would need the help of clinic staff in accessing the files, but argued that this cost was small in relation to the benefits of her study. She pointed out that she and her researchers are clinically trained (and registered with

the Health Professions and Social Work Councils) and thus in a position to provide useful feedback to the clinic on patients who were deemed to be at risk for poor adherence owing to their mental health and social difficulties. She also pointed out that some of the empirical indicators being developed in her study could potentially become useful tools for the counsellors associated with the treatment programme to use in the future should they wish to assess the extent to which a patient's psychological well-being places them at risk for poor adherence: 'More broadly, the research aims to make *recommendations about the kinds of psychosocial services* which can enhance women patients' quality of life and psychological well-being, as well as *enhancing their adherence* to treatment' (student research protocol).

The student approached a clinic in a local African township for permission to invite potential respondents to participate in her study. The medical practitioner/researchers associated with the antiretroviral treatment project at the clinic considered her request – but rejected it. As can be seen from the three reasons listed below, the fact that the research and treatment intervention was funded in part through a large pharmaceutical company seemed to pose particular problems.

1. 'The population is over-researched and your study is not the primary focus of the research' ('the research' referring, of course, to the research already being conducted by the medical doctors/researchers linked to the clinic);
2. 'None of the (*pharmaceutical company*) Exco members are senior authors of the project' (i.e. the student's doctoral project); and
3. 'It has not been approved by the same Ethics Committee as the other (*pharmaceutical company*) projects' (written response to the student).

The student was then referred to another clinic in a different African township, but was again turned down by the gatekeeper committee of medical practitioner/researchers. This time she was turned down principally because:

1. There were insufficient 'direct and tangible benefits to the clinic patients';
2. They were concerned about the 'amount of time' respondents would have to spend on the study; and
3. They did not 'feel that the research addresses the needs which they have as a clinic at this point in time, and only want to permit research which does so' (response to the student).

The student responded to the main research gatekeeper of this clinic by reiterating that her research could be of potential direct and immediate benefit to the counsellors who work with people on antiretroviral treatment as well as to the patients themselves: 'Depending on the clinic's need, feedback from the research could either be restricted to liaising with the counselling team, or direct input could also be given to the other members of the clinic team if relevant and useful. Whichever approach minimises the negative impact of our presence on the running of the service, while maximising the support and benefits, is desirable for me' (response by the student).

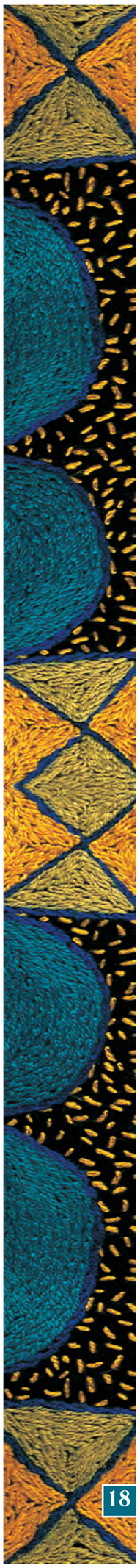
She never got a reply to this correspondence. She made several phone calls (all to no effect) and eventually gave up. Fortunately, a local clinic run by Absolute Return for Kids (ARK) came to the rescue and let her conduct her research there. The fact that it was not linked to either a pharmaceutical company or a major research project no doubt helped ...

This story of her rejection by the first two clinics is interesting in several respects. Firstly, with regard to both clinics she approached, the medical practitioner/researchers prioritised their own research interests and used their effective control over the clinic to prevent other research from taking place. The blocking of research by the first clinic on the grounds that only research linked to the pharmaceutical company that was funding it would be acceptable was breath-taking in its blatant self-interest.

Secondly, it is clear from the reasons provided by the second clinic that non-medical interventions were not regarded as potentially being of value to the patient. This reflects an uncritical adoption of a strictly biomedical notion of health promotion which is particularly worrying given the obvious social and psychological determinants of adherence to antiretroviral therapy. It also demonstrates a lack of understanding that even when the 'benefits' of social science research for a particular individual patient are not obvious, the research may nevertheless inform the development of relevant future social policies. A narrow application of the requirement that the research 'benefits' the research subject is therefore necessarily always going to be biased against the social scientist.

Thirdly, the story demonstrates a paternalistic approach on the part of medical practitioner/researchers to who is in the best position to judge whether a project is, or is not, in the best interests of the patient. This, in my view, runs counter to the spirit of the principle of informed consent. Although the principle of informed consent was designed to ensure that prospective research subjects have the right to refuse to participate, it surely also protects these same subjects from others deciding on their behalf that it is not in their best interests to participate. The principle should surely be that research subjects have the right to decide whether they want – or do not want – to participate. In my experience of conducting surveys and qualitative in-depth interviews, research subjects often enjoy being interviewed and having the opportunity to discuss matters of concern to them (see also Pahl[1]). This is, of course, not true for all participants. Some get irritated by the research process, but they can always refuse to participate at any point (as is typically – if not always – pointed out in consent forms).

Ultimately, it must be up to the potential research participant to decide whether the risks (which, in social science research, typically entail little more than the opportunity cost of the time taken up by the interview) outweigh the benefits. Medical



practitioner/researchers are not in an appropriately informed position to make the judgement call.

SOME ETHICAL CONCERNS

Most research ethics codes are silent on the issue of ensuring that potential research subjects have the right to choose whether they do or do not want to participate in research. The European Group on Ethics in Science and New Technologies[2] and the Nuffield Council on Bioethics (UK)[3] note that in some local contexts, it may be appropriate to obtain family- or community-level agreement before approaching research subjects (see discussion in NCOB,[4] p. 73). However, this is a concession to local culture – it cannot be used to justify giving medical practitioner/researchers the right to make decisions on the behalf of their patients, especially in cases where these same medical practitioner/researchers are not disinterested observers.

Before 1947, when the Nuremburg code of ethics for medical research highlighted the need for informed consent,[5] the prevailing 'Hippocratic' approach assumed that medical researchers and doctors were the only agents capable of making appropriate judgements about medical research.[6] Refusing to allow patients on antiretroviral therapy the opportunity to make their own decision as to whether they wish to participate in a psychological study or not amounts to a reversion to this old paternalistic approach.

Some attention has been paid to the problem of 'dual loyalty' – i.e. when a clinician experiences a role conflict between their professional duties to a patient and the obligations, expressed or implied, real or perceived, to the interests of a third party (see Physicians for Human Rights and University of Cape Town Health Sciences Faculty[7]). However, as Singh points out,[8] this problem has yet to be applied to dual loyalty in medical research – especially when the roles of clinician and researcher merge: 'In the practice-research context this translates to the physician-researcher's primary interest (duty of care towards the patient-subject) being undermined by secondary factors (such as loyalty to the study/sponsor)' (p. 395). Furthermore, clinicians may deny social scientists access to 'their' patients not because they are worried about the adverse implications of the social science research for the patients, but because they do not want any other research (besides their own) being conducted on the patients.

Disciplinary differences like this would not matter except for the fact that medical practitioner/researchers are in a powerful position to dictate the research agenda largely because they have access to extraordinarily large budgets to treat and research their patients. In a very real sense, these medical practitioner/researchers do indeed control 'their' patients/research subjects – and as discussed above, they can use this power and deny others research access to them.

With about a fifth of the adult population HIV-positive, and given the government's reluctance to roll out antiretroviral therapy with any sense of urgency, there is substantial pressure (both in terms of resources and emotional energies) on HIV clinicians. Their irritation with social science research is therefore in some way understandable. However, as the AIDS crisis is both a social and health crisis, and given that social scientists are often better placed than medical practitioners to understand the social and behavioural context governing individual adherence to antiretroviral therapy, the effective control of medical practitioner/researchers over access to research subjects is highly problematic. There needs to be a more tolerant and constructive attitude towards social science research on the part of HIV clinicians who control access to patients on antiretroviral therapy.

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ERRATUM

There was an error in the article entitled 'Staging of HIV disease in children – towards pragmatism?', which appeared in the November 2005 issue of the *Journal* (issue 21). In Table II (p. 16), hepatosplenomegaly should have been listed as a stage 2 and not a stage 1 event.

DRUG REACTIONS AND THE SKIN IN HIV/AIDS

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Drug reactions are common in HIV-positive individuals, approximately 100 times as common as in the general population, and they increase with increasing immunodeficiency.[1] Factors associated with drug reactions in HIV disease are polypharmacy to deal with opportunistic infections, the nature of drugs prescribed for AIDS-related illnesses, slow acetylator status, relative glutathione deficiency, CD4 count < 200 cells/µl and > 25 cells/µl,[2] latent cytomegalovirus and Epstein-Barr virus infections[3] and high CD8+ cell counts (> 460 cells/µl).

The majority of reactions involve the following agents:

- trimethoprim-sulfamethoxazole
- other sulfonamide drugs, and
- various penicillins.

These drugs account for 75% of all adverse drug reactions. Trimethoprim-sulfamethoxazole adverse reactions are the commonest, the prevalence increasing from approximately 2 - 8% in the general population to 43% in HIV-positive individuals and to approximately 69% in patients with AIDS.[4-6] One reason suggested for the striking incidence of reactions to trimethoprim-sulfamethoxazole is the systemic glutathione deficiency in individuals with HIV/AIDS, which increases the likelihood of accumulation of toxic intermediates such as the hydroxylamine derivatives in the circulation, hence inciting adverse drug reactions.[7] Other agents implicated are antituberculosis drugs, antiretrovirals, non-steroidal anti-inflammatory drugs (NSAIDs) and anticonvulsants.

DIAGNOSIS OF ADVERSE CUTANEOUS DRUG REACTIONS (ACDRs)

A thorough knowledge of the presentation, identification and management of ACDRs is important, since they are a significant cause of morbidity and mortality. They most commonly present as a morbilliform eruption 7 - 14 days after the initiation of therapy, which resolves after withdrawing the offending agent. The rash may present as an itchy, symmetrical, fine, erythematous, maculopapular eruption on the trunk, sparing the face and worse in the intertriginous areas (Fig. 1). Other features are fever, headache, myalgia, arthralgia, granulocytopenia, thrombocytopenia and raised liver enzymes. Histological examination of the skin reveals a superficial perivascular infiltrate of lymphocytes and histiocytes, with vacuolar interface changes and spongiosis.[3] The morbilliform eruption occurs in 95% of cutaneous adverse drug reactions,[8] with other types listed below.

TYPES OF ACDR

- Morbilliform: erythematous maculopapular rash, measles-like (Fig. 1).
- Erythema multiforme: erythematous iris-shaped papules and vesicobullous lesions on extremities and mucosal surfaces (Fig. 2).
- Urticaria/angioedema: erythematous itchy wheals sometimes with lip and tongue swelling.
- Fixed drug eruption: dusky round macules with blistering which heal with hyperpigmentation (Fig. 3).
- Lichenoid eruption: itchy, violacoeus eruption similar to lichen planus, healing with dusky grey pigmentation.
- Vasculitis: palpable purpura accentuated on extremities.
- Stevens-Johnson syndrome (SJS): erythema multiforme lesions involving two or more mucosal surfaces; may occur with skin exfoliation less than 10% of the total body surface area (Fig. 4, a, b, c).
- Toxic epidermal necrolysis (TEN): a syndrome which begins with erythema and tenderness of the skin and progresses to stripping of the skin of more than 30% body surface area (Fig. 5, a, b, c).

LIFE-THREATENING ACDR

It is vital to look for the following signs of life-threatening ACDR:

- Confluent erythema, palpable purpura, blisters, skin necrosis and mucosal erosions.

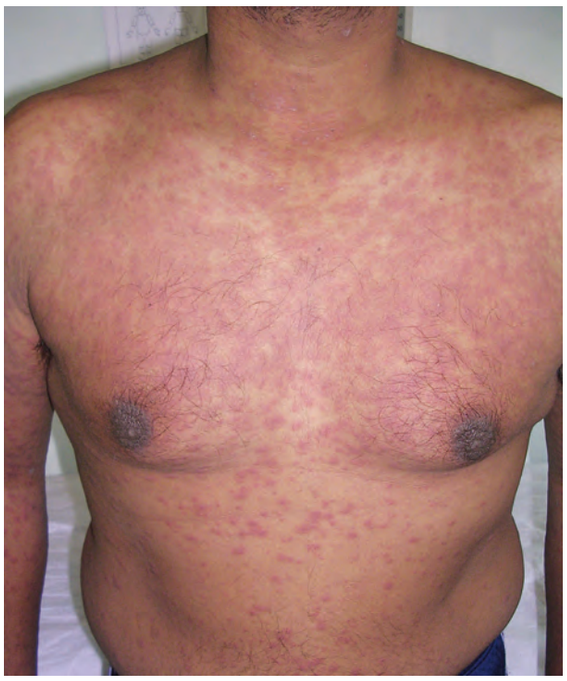

Fig. 1. Morbilliform rash.

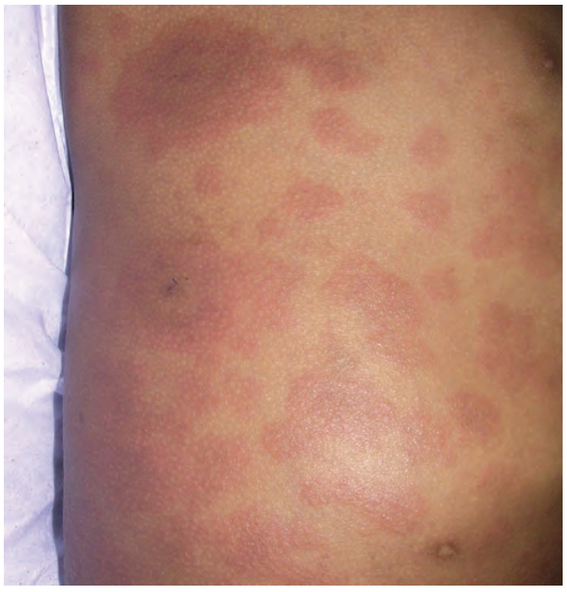

Fig. 2. Erythema multiforme: urticarial plaques with targetoid centres.

- Urticaria, tongue swelling, dyspnoea, wheezing, hypotension.
- Fever (temperature over 40°C), enlarged lymph nodes, arthralgia/arthritis, eosinophilia (> 1 000/µl), lymphocytosis with atypical cells, and abnormal liver function test (LFT) results, i.e. > 5 times the upper limit of normal (ULN).

ACDRs TO CO-TRIMOXAZOLE

This is the commonest ACDR in HIV infection. The prevalence in the general population is 2.6 - 8%, increasing 10-fold in HIV infection. It rises from 43% in HIV infection to 69% in AIDS.[4-6] At least 50 - 60% of patients will experience a morbilliform reaction with associated fever 1 - 2 weeks after initiating therapy. If the reaction is non-life-threatening, therapy can be continued with symptomatic treatment using systemic antihistamines and topical corticosteroids for the rash. It is important to carry out regular assessment and patient education for danger signs. If the rash persists, the dose of co-trimoxazole should be reduced. If this is still ineffective, corticosteroids (0.5 mg/kg) should be prescribed up to a maximum of 21 days.

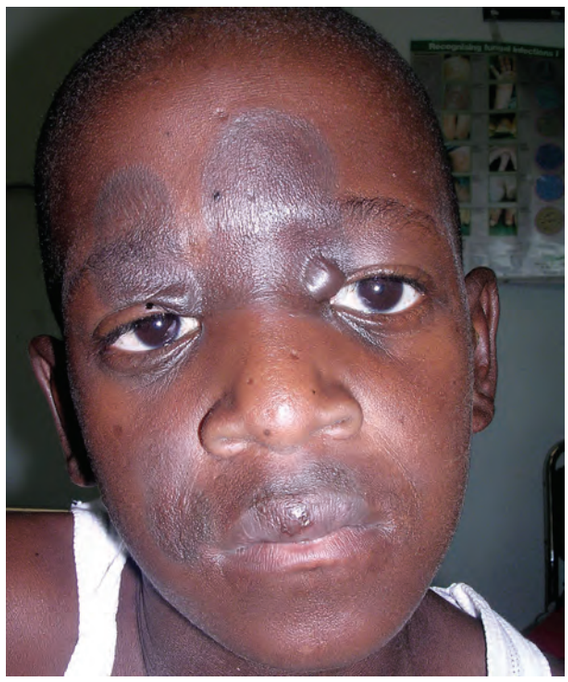

Fig. 3. Fixed drug eruption.

Re-challenge is safe in patients with non-life-threatening hypersensitivity.[9] Desensitisation of patients with documented, non-life-threatening ACDR has been shown to effectively induce tolerance in 63% of cases.[10] Patients requiring re-challenge and desensitisation should be referred to a tertiary centre.

ACDRs TO ANTITUBERCULOSIS THERAPY

Historically, severe cutaneous hypersensitivity has been an extremely rare complication of antituberculosis chemotherapy in TB patients in Africa. However, there has been an increase in cutaneous reactions in HIV-infected patients on tuberculosis (TB) therapy, reported to occur in 23% of patients in one series.[11] Reactions are usually morbilliform and may be severe, and are commonest against thiacetazone, followed by streptomycin, para-aminosalicylic acid (PAS) and isoniazid (INH). However, reactions to antituberculosis therapy are common in HIV-infected patients even when using thiacetazone-free regimens.

If reactions are minor and self-limiting, symptomatic therapy may be all that is required. If persistent, stop all treatment and identify the drug(s) responsible, and try to resume therapy as soon as possible.

Fig. 4 (a). Stevens-Johnson syndrome: conjunctival erosions.

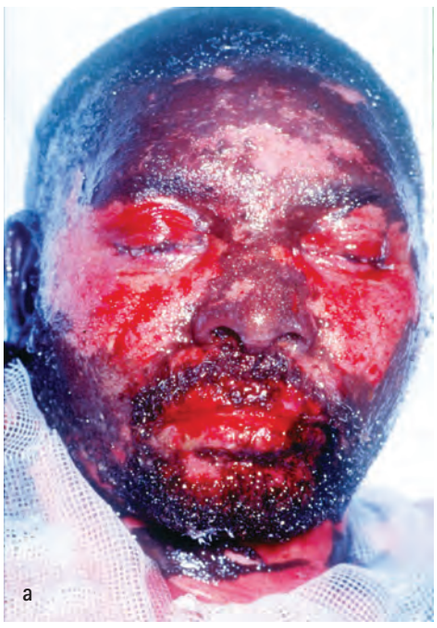

Fig. 5 (a). Toxic epidermal necrolysis: generalised stripping of the skin.

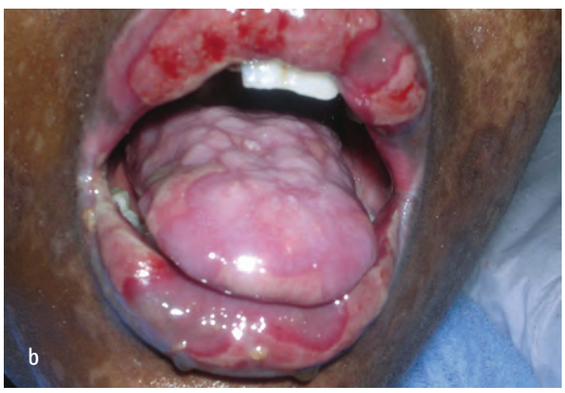

Fig. 4 (b). Stevens-Johnson syndrome: oral erosions.

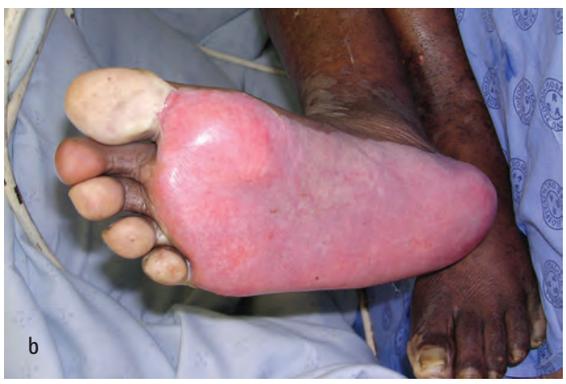

Fig. 5 (b). Toxic epidermal necrolysis: stripping of skin of sole.

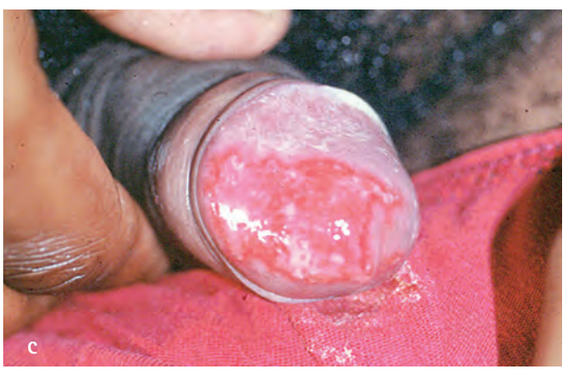

Fig. 4 (c). Stevens-Johnson syndrome: penile erosions.

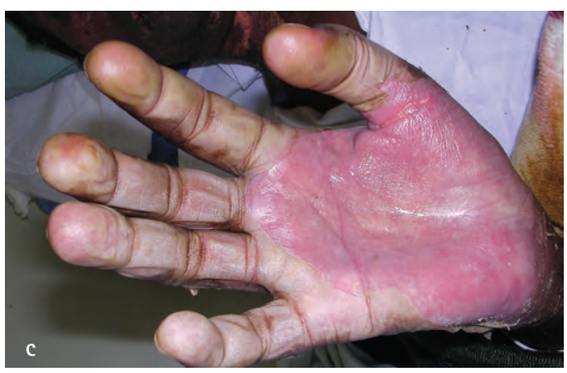

Fig. 5 (c). Toxic epidermal necrolysis: stripping of palmar skin.

To re-challenge, after the reaction subsides daily challenge doses should be administered. Aim to start with those drugs least likely to be implicated (Table I), and if there is no reaction to challenge doses, continue with full doses.

ACDRs AND HAART

ACDRs are common with antiretroviral (ARV) drugs, especially with the non-nucleoside reverse transcriptase inhibitors (NNRTIs), but can occur with all ARVs. Most reactions are morbilliform and non-life-threatening, and the majority will resolve despite continuation. They are commonest with the NNRTIs, nevirapine (NVP) and efavirenz (EFZ) and usually occur within the first 4 - 6 weeks. They most commonly present with a morbilliform eruption or urticaria and occur in 9 - 32% of patients on NVP. The major risk factors for NVP rash are female gender, HLA DRB1*0101, and high CD4 count (> 250 in females and > 400 in males). However, in the

TABLE I. ANTI-TUBERCULOSIS DRUG RECHALLENGE REGIMEN*

Drug	Day 1	Day 2	Severe reaction (1/10 dose)
INH	50 mg	300 mg	5 mg
RIF	75 mg	300 mg	7.5 mg
PZA	250 mg	1.0 g	25 mg
ETH	100 mg	500 mg	10 mg
STREP	125 mg	500 mg	12.5 mg
PAS	1.0 g	5.0 g	0.1 g

INH = isoniazid; RIF = rifampicin; PZA = pyrazinamide; ETH = ethambutol; STREP = streptomycin; PAS = para-aminosalicylic acid.
* Girling DJ. Adverse effects of antituberculosis drugs. *Drugs* 1981; **23**: 56-74.

absence of blisters, erythroderma, mucosal involvement and hepatitis, therapy can be continued and the reaction treated symptomatically with antihistamines and corticosteroids. Approximately 6 - 7% of patients will require discontinuation. Signs indicating that treatment should be stopped are:

- mucosal involvement, blistering and exfoliation
- clinically significant hepatic dysfunction, temperature of 39°C or higher and intolerable pruritus.

SJS (Fig. 4, a, b, c) and TEN (Fig. 5, a, b, c) occur in approximately 1% of treated patients and require prompt recognition and permanent discontinuation of the drug. In these patients reintroduction is contraindicated. Close monitoring of patients on NVP is therefore essential in the first 8 weeks after initiation of therapy. Patients who develop a rash should always be assessed for hepatotoxicity.

HYPERSENSITIVITY SYNDROME

This is a life-threatening reaction that occurs in the first 42 days of ART. It presents with a diffuse maculopapular eruption, fever, eosinophilia, atypical lymphocytosis, multivisceral involvement and abnormal LFT results (AST and ALT > 5 X ULN) and occurs most commonly with NVP (2%), EFZ, abacavir (ABC), amprenavir and indinavir. The mortality rate is 10% with NVP, death usually being due to liver failure. If hypersensitivity is suspected, discontinue without re-challenge.

RECURRING DRUG REACTIONS

Persistent non-life-threatening drug reactions or recurrent reactions can seriously impede effective management of HIV and opportunistic infections. These reactions occur during the first 8 weeks of therapy, coinciding with the increase in CD4+ cell count, and are a manifestation of immune reconstitution. The use of a protracted course of steroids (0.5 mg/kg for the first 8 weeks of therapy) in patients who develop recurrent and potentially severe cutaneous eruptions and have a past history of ACDRs allows suppression of reactions while initiating and continuing crucial medications.[12]

CONCLUSION

ARV therapy has significantly reduced overall mortality from HIV. In patients on highly active antiretroviral therapy (HAART) cutaneous manifestations of HIV have been reduced by 40%[13] and dermatological consultations by 63%,[13] and the resultant burden of disease from inflammatory, infective disorders and malignant disease has also been reduced, enabling patients to enjoy a better quality of life. The incidence of cutaneous drug reactions has increased from 8% to 20%,[13] the most severe reactions being SJS, TEN and hypersensitivity syndrome. These severe life-threatening adverse cutaneous reactions occur most commonly with the NNRTIs, NVP and EFZ; the NRTI ABC, and the protease inhibitors (PIs) indinavir and amprenavir. Most reactions (86%) occur within 4 weeks of therapy and require prompt recognition and treatment discontinuation without re-challenge, and appropriate drug substitution.

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REVISED GUIDELINES FOR DIAGNOSIS OF PERINATAL HIV-1 INFECTION IN SOUTH AFRICA

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These guidelines for best practice under both ideal and resource-constrained conditions are intended to provide guidance for health care professionals regarding the laboratory diagnosis of HIV-1-infected infants and young children. Resources, circumstances and decisions will differ across the wide range of clinical settings occurring in southern Africa and other developing countries. These serve as an update of guidelines published in this journal in 2001.[1]

The diagnosis of HIV-1 infection in infants begins with identifying HIV-1 infection in women before and during every pregnancy; this awareness should also identify the infant at risk for HIV-1 infection.[2,3] Nonetheless, perinatal HIV-1 diagnosis presents challenges such as:

- Difficulty in establishing an early and rapid diagnosis in exposed infants due to the persistence of transplacentally acquired maternal IgG HIV-1 antibodies. These may remain present in the blood for 15 - 18 months.[4]
- Timing of HIV-1 transmission from mother to child, which directly affects the sensitivity and specificity of available HIV-1 diagnostic assays.
- The risk of the infant being exposed to HIV-1 throughout the duration of breastfeeding.
- Whether to use quantitative and/or qualitative HIV-1 nucleic acid-based virological assays.
- The utility and role of detecting p24 antigen for diagnosis and prognosis.
- The global existence of multiple clades or subtypes of HIV-1 and its effect on assay performance.[5-10]

Clinical acumen should prevail in interpreting HIV-1 test results; for example, HIV-1 infection can be ruled out in children ≥ 18 months of age with negative HIV-1 serology, a history of either no breastfeeding or breastfeeding that ceased at least 6 weeks previously, no clinical symptoms of HIV-1 disease and no hypogammaglobulinaemia.[4] Rapid HIV tests should perform as well in children >18 months as in adults. Algorithms are in the process of being validated locally.

In turn, all women should be encouraged to undergo voluntary counselling and testing (VCT).[2] As per National Treatment guidelines for infants,[11] testing may only be conducted on infants following pre-test counselling and only once informed consent has been obtained from parents, legal guardians or primary caregivers. This document should be read in conjunction with the testing algorithm summarised in Fig. 1.

INTRODUCTION

The need for expanded testing practices for the early diagnosis of HIV in exposed infants is now well established, hence the urgent need for review of these infant diagnostic guidelines. Early diagnosis is critical to facilitate:

- comprehensive care of infected children including ARV treatment
- evaluation of prevention of mother-to-child transmission (PMTCT) programmes, and
- added social benefits such as a reduction in maternal anxiety,[12] stratification of health care services, and recommendations for appropriate infant feeding practices.

HIV-infected children under 24 months of age are a particularly vulnerable group. A recent natural history study showed that approximately 35% of infected children in Africa died before 1 year of age and that more than 52% have died by their 2nd birthday.[13] Early diagnosis has the potential to reverse this situation, provided that primary care services are adequately capacitated to provide these children with appropriate care including nutritional support, co-trimoxazole prophylaxis, clinical and CD4 count monitoring and timely referral for antiretroviral therapy.

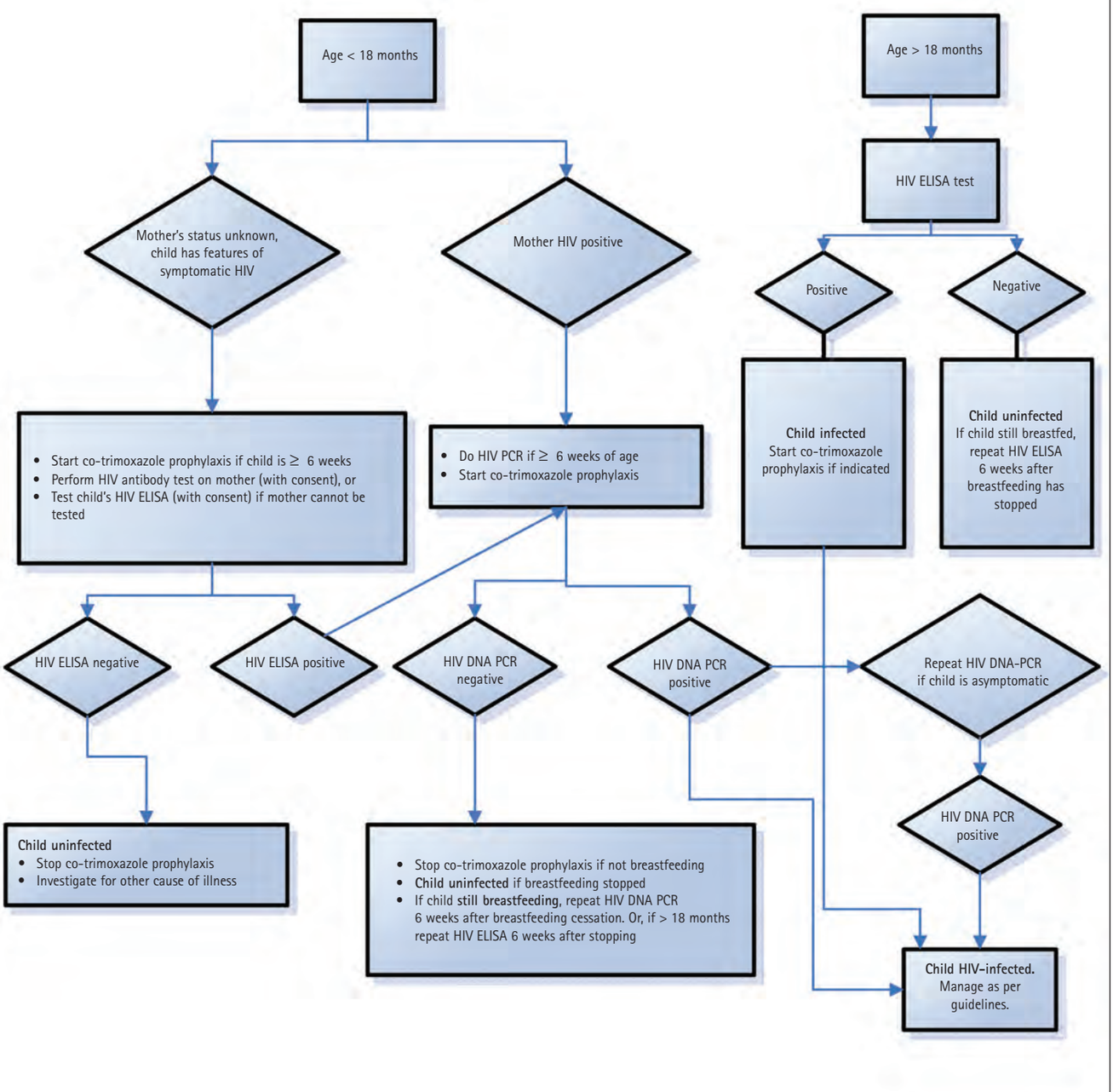
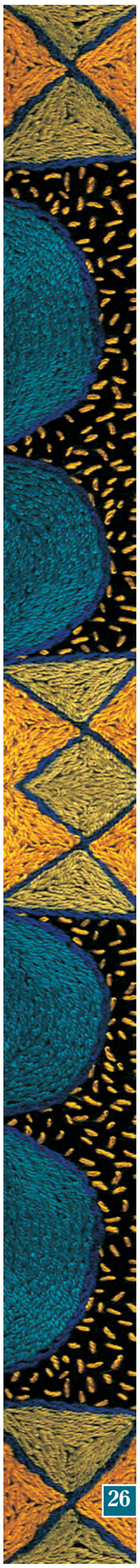


Fig. 1. HIV infant testing algorithm (modification of the testing algorithm from the National Department of Health, National Antiretroviral Treatment Guidelines, *1st ed., April 2004).*



Based on recent antenatal HIV prevalence figures of 29.5%[14] and assuming there are a million births per year in South Africa, approximately 300 000 infants require access to early diagnosis. Previously, protocols in resource-poor settings have recommended that infants be followed up for 1 year on co-trimoxazole prophylaxis from 6 weeks of age and then tested using HIV enzyme-linked immunosorbent assay (ELISA) testing strategies at 12 months of age. The reality of this practice is illustrated by experience in Johannesburg, South Africa, where over 60% of infants were lost to follow-up by 6 weeks and 85% by 12 months of age during a 24-month period (October 2001 - September 2003).[15,16] The absence of a diagnosis, and the death of 40% of HIV-infected infants by 12 months of age, severely limits children's access to comprehensive care.[17] Furthermore, a diagnostic algorithm incorporating a single HIV DNA polymerase chain reaction (PCR) test at 6 weeks of age costs society less than one that uses an HIV ELISA test at 12 months of age.[18]

Much emphasis has been focused on choosing the appropriate technology to allow for timeous diagnosis. Important considerations include:

- sample volume
- mode of specimen collection
- required turnaround
- laboratory technical skills, and
- cost.

Recent work in Johannesburg has confirmed the potential value of two diagnostic assays for early infant diagnosis of HIV:

- Roche HIV DNA PCR assay version 1.5, and
- the ultrasensitive heat-denatured p24 antigen quantitation assay.[19]

In summary, 627 non-breastfed HIV-exposed infants (58 HIV positive) had their HIV status determined according to Centers for Disease Control (CDC) guidelines. A single HIV DNA PCR using the Roche Amplicor assay version 1.5 at 6 weeks of age had a sensitivity of 98.8% and specificity of 99.4%.[20] The use of the 6-week visit coincides with the first immunisation visit and thus fits in well with the continuum of care.

The performance of the Roche HIV DNA PCR assay has been confirmed in other regions as summarised in Table I.

Data on the second option, the ultrasensitive heat-denatured p24 antigen assay at 6 weeks, yielded satisfactory results in South Africa with a sensitivity and specificity of 97.7% and 100% respectively when compared with HIV DNA PCR testing.[25] The performance of this assay for infant diagnosis has been confirmed in other studies and is summarised in Table II.

TABLE I. SUMMARY OF PERFORMANCE OF ROCHE AMPLICOR HIV DNA PCR ASSAY VERSION 1.5 IN DIFFERENT SUBTYPES

Region	Prevalent subtype	Sensitivity and specificity	Reference
Zimbabwe	C	100%; 100%	Zijenah *et al.*[21]
Tanzania	A, C, D		Lyamuya *et al.*[22]
Rwanda	A	100%; 98%	Fischer *et al.*[23]

TABLE II. SUMMARY OF PERFORMANCE OF ULTRASENSITIVE HEAT-DENATURED P24 ANTIGEN QUANTITATION ASSAY FOR INFANT DIAGNOSIS OF HIV

Region	Prevalent subtype	Sensitivity and specificity	Reference
Tanzania	A, D	99%, 100%	Lyamuya *et al.*[26]
Switzerland; US	B	97 - 98% sensivity/ 98 - 99% specificity	Nadal *et al.*;[27] Respess *et al.*[28]
Thailand and Cambodia	E	97 - 98% sensitivity/ 97 - 99% specificity	Sutthent *et al.*,[29] Nouhin *et al.*[30]

In remote settings, difficulties have been experienced with sample collection and transport for infant diagnostic specimens. This has been overcome with the use of dried blood spots followed by extraction and the Roche HIV DNA PCR assay. The Roche HIV DNA version 1.5 PCR assay performed on unmodified filter paper at 6 weeks of age yielded an accurate diagnosis of HIV infection with a sensitivity and specificity of 100% and 99.6% respectively compared with PCR conducted on whole-blood samples.[31] Preliminary data suggest that DBS from capillary (e.g. heel prick) versus venous blood also yields highly accurate HIV DNA PCR results (personal communication – G Sherman). The ultrasensitive p24 ag assay has recently been modified for use on dried plasma[32] and dried blood spots.[33]

In the South African context, owing to the sheer numbers of samples needing diagnosis, automated testing methodologies for assays such as the Roche HIV DNA PCR assay have been explored. To date the automation of the extraction method for this assay has been optimised using the Roche MagNapure Analyser. When comparing this approach with the conventional whole-blood manual extraction method 100% concordance was noted (W Stevens – personal communication). This method also reduced the number of equivocal results and internal control failures to 1 - 2% of samples run. Preliminary data suggest that this method works well for dried blood spots using the MagNapure LC DNA Isolation kit III (W Stevens – personal communication) and the data will be published shortly.

DEFINITION OF AN HIV-1-UNINFECTED INFANT/CHILD

A child should not be labelled as HIV positive simply if the mother is HIV positive; the correct terminology in this situation is HIV-exposed.

An HIV-1-uninfected infant/child can be defined as an infant/child with a negative HIV-1 serological or virological test

where clinical features are not discordant. The following modifiers apply to age categories:

- For children older than 18 months of age a negative HIV-1 serological test based on the ELISA method confirms absence of HIV-1 infection, provided that breastfeeding ceased at least 6 weeks before the first test.
- For infants between 6 weeks and 18 months of age, one negative HIV DNA PCR test result indicates non-infection provided that breastfeeding ceased at least 6 weeks before the test. Confirmation of an infant's HIV infection status using an HIV ELISA test at 15 - 18 months can be done.

DEFINITION OF AN HIV-1-INFECTED INFANT/CHILD AND RECOMMENDATIONS ON THE USE OF HIV TESTS

HIV-1 diagnostic techniques are more difficult to interpret in infants and young children than in older children or adults because of the persistence of maternal antibodies up to 12 - 18 months of age. The HIV-1 DNA PCR detects the integrated HIV virus DNA ('provirus') into the genome of mononuclear cells, and is considered the test of choice for establishing the diagnosis of perinatally acquired HIV-1 infection.[34] This PCR is a diagnostic qualitative reaction, distinct from the RNA quantitative reaction (viral load test) used for the prognostic staging or clinical monitoring.[35] The HIV-1 DNA PCR is a rapid and accurate method for identification of HIV-1 infection in infants and young children under 18 months of age. Currently the only assay with extensive validation in South Africa is the Roche Amplicor DNA assay version 1.5. However, PCR amplification is prone to contamination and testing should take place strictly according to the manufacturer's instructions and only in areas dedicated for PCR work. HIV-1 DNA PCR methods are considered reliable when standardised and performed in laboratories following good laboratory practices.

These tests have been accurate for all known HIV-1 subtypes but ongoing molecular surveillance is necessary to confirm their performance for novel subtypes.

- An HIV-1 DNA PCR test should be performed on infants between 6 weeks and 18 months of age for diagnosis. If the HIV-1 DNA PCR is positive infection is established, and if the infant is currently being breastfed this may be continued and the infant should receive prophylaxis for opportunistic infections such as *Pneumocystis jiroveci*.
- Infants under 6 weeks of age presenting with clinical features suggestive of HIV infection should have an HIV-1 DNA PCR test performed. Infants with rapidly progressive disease require early initiation of antiretroviral therapy and may die if the PCR test is delayed. Should this test be negative, a repeat test is recommended at or after 6 weeks of age
- In infants over 18 months of age, a positive HIV ELISA assay as per the national testing algorithm confirms diagnosis of HIV infection.
- Whenever clinical features are discordant with HIV test results, re-testing is indicated.

DETERMINATION OF HIV INFECTION IN ABANDONED/ORPHANED INFANTS

- Perform an HIV ELISA to assess HIV exposure at birth if results for the mother are not available. If you have confirmation of a positive HIV ELISA result for the mother this test may be omitted.
- If HIV antibody assay for mother or infant is positive, perform an HIV DNA PCR assay at 6 weeks. This may be repeated on a second sample at any stage to confirm the 6-week result and comply with the HIV testing requirements of adoption agencies.

LEGISLATION REGARDING HIV TESTING IN INFANTS

The final version of the Bill is not yet available but will be shortly and posted at **http://www.gov.za** and called the Children's Act. In summary, the following important information will be included:

- Informed consent to HIV testing may be obtained from a child aged 12 years or older without the assistance of the parents/caregivers provided the child is sufficiently mature to understand the implications of the test. If the child is under 12 years of age but is sufficiently mature to understand the implications of the test, consent may be obtained without the assistance of parents/caregivers.
- If the child is under 12 years of age and cannot understand the implications of the test, and has no parents and caregivers, consent is to be obtained from the provincial head of social development.
- If the child is under 12 years of age and not mature, options are as follows:
  - the child protection agency arranging the placement of the child can consent, or
  - the medical superintendent/person in charge of the hospital – if no parents/caregiver and no child protection agency is involved, or
  - the children's court – if consent is being withheld (by anyone capable of giving consent, not just parents) or if child and parents are not able to give consent.
- In the case of an abandoned child who has obviously been deserted by parent/s, legal guardian or caregiver or who has had no contact with parent/s, legal guardian or caregiver for 3 months for no apparent reason, a caregiver may give consent. A caregiver is defined as the individual who actually cares for a child and may include a foster parent, kinship carer, person who cares for a child in temporary safe care, head of shelter, child protection or youth agency, child or youth care worker who cares for a child without appropriate care in the community, and child who is head of a child-headed household.
- Consent to HIV testing also cannot be withheld unreasonably.

OTHER POINTS TO CONSIDER

- In South Africa, the quantitative HIV RNA (viral load) test has not been validated as a diagnostic tool but should be reserved for assessing prognosis and further management of the patient. The reasons for this recommendation include the following:
  - workflow issues within local laboratories, and
  - delayed transport from remote areas causing deterioration of RNA.
- The measurement of HIV-1 p24 antigen in blood is sensitive enough for early diagnosis of HIV infection in infants and young children only if the ultrasensitive heat-denatured p24 antigen quantitation assay described by Schupbach and colleagues. (Ledergerber *et al.*[19]) is used. Until a consistent reagent and buffer for this assay have been obtained, it should not be widely used.
- Whether to test all infants at 6 weeks of age or delay testing in breastfed infants until 6 weeks after breastfeeding has ceased, remains controversial.
- The current national diagnostic algorithm recommends antibody tests after 18 months of age despite the fact that many uninfected infants serorevert (lose maternal HIV antibodies) between 9 and 12 months of age. It is reasonable to use HIV antibody tests earlier than 18 months of age provided health care workers understand that a positive HIV ELISA test under 18 months of age may indicate HIV exposure and not HIV infection.

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ALL CD4s THAT FLITTER DO NOT FOLD

To the Editor: In South Africa the prevalence of HIV infection is around 14%[1] with over 6 million infections. Health care workers as well as the public tend to blame HIV infection for a variety of ills. Any individual who is suffering from recurrent infections or loses weight is suspected of being infected. However, the protocol for diagnosis of HIV in adults is that a specific diagnostic test must be done and confirmed before informing the patient of the diagnosis.

Gauteng has about 1.5 million infections, accounting for about 23% of all South African infections.[1] The national antiretroviral (ARV) rollout component of the Department of Health's Comprehensive Plan started in this province in April 2004. One of the sites, situated at Helen Joseph Hospital in Johannesburg, is up and running with over 2 000 patients enrolled on its programme to date. HIV-positive patients are referred to the ARV clinic for initiation of treatment from a number of sources, including the antenatal clinics, self-referrals and private practitioners, but mainly from the hospital itself. After the patients have attended a wellness programme explaining basic HIV knowledge, a CD4 count is done. Those who need ARVs are then are asked to attend a session on adherence, followed by an appointment with the doctor. Ill patients, those with very low CD4 counts and pregnant women are 'fast-tracked' through the process.

In October 2004, a 32-year-old woman was referred to us from the hospital after having had two admissions. She had a CD4 count of 75 cells/µl (normal > 600), with a percentage of 20.1%. This indicates lymphopenia and not specifically a decrease in the CD4 subset. She had been admitted with symptoms of weakness and dyspnoea and had been given a transfusion. She had no rash or joint pains, and had been discharged on prednisone 30 mg/d. She stated that she had been tested for HIV at the last admission.

In checking her results, we confirmed that she had been admitted in January 2004 with a haemoglobin concentration of 5.3 g/dl with normal red cell indices. The peripheral smear showed autoagglutination, spherocytes, diffuse basophilia and occasional nucleated red blood cells. The reticulocyte production index was normal, indicating an adequate marrow response. A bone marrow aspirate and trephine showed a hypercellular marrow primarily due to erythroid hyperplasia. She had a positive direct Coombs test. Other evidence of haemolysis was a lowered haptoglobin and an increased lactate dehydrogenase. She was transfused with two units of packed cells. She was readmitted in July 2004 with a similar picture, and at this admission autoimmune tests were done. Her antinuclear antibody was positive with a titre of 1 in 320 with a speckled pattern. She therefore had features of active haemolysis with some autoimmune features.

In her outpatient notes the next month a medical officer wrote a diagnosis of RVD (retroviral disease) and autoimmune haemolytic anaemia. She was then referred to our clinic.

As there was no record of her HIV test result we conducted a rapid test, confirmed by a laboratory enzyme-linked immunosorbent assay. Both the tests were negative.

As an addendum, I told the patient that she did not have HIV but an autoimmune condition. She asked me if there was a cure for this new disease. When I answered in the negative, she said, 'What is the difference, I still have an incurable illness.'

A CD4 cell count repeated in November 2004 was 602 cells/µl with a percentage of 22.1.

Even in a country with a high HIV incidence and prevalence, it is important to follow normal practice and confirm the diagnosis. A CD4+ count is a surrogate marker and does not confirm the diagnosis. Most low CD4 counts in South Africa are due to HIV infection, but there are other possibilities. These include infection with HIV-2, HTLV-1, HTLV-2 or other mononuclear trophic viruses and idiopathic CD4 T-cell lymphopenia, as well as autoimmune conditions.[2]

A parallel situation is that a raised carcinoembyonic antigen level does not confirm the diagnosis of a bowel malignancy but is a surrogate marker. The diagnosis of a malignancy is a histological one.

This is the second time an underlying autoimmune condition has been misdiagnosed as HIV infection in our clinic. An ill-appearing, wasted patient with an extensive skin rash was referred to us after having been started on ARVs in Northern Province 3 months earlier. She was not improving so was sent to us for other investigations. She was HIV negative and was subsequently diagnosed with systemic lupus erythematosus. I was also asked to start an emaciated patient on ARVs by his family after he was diagnosed with TB. He also was HIV negative and has done well on TB treatment. We have heard of other anecdotal cases of HIV-negative patients being started on ARVs because they fit the 'typical' AIDS profile.

Doctors should not become lazy in making a diagnosis. A rapid HIV test should be done to confirm the diagnosis if there is any doubt at the point of care.

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ANTIRETROVIRAL DRUG RESISTANCE: A GUIDE FOR THE SOUTHERN AFRICAN CLINICIAN

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Both private and public sector see a bewildering clinical array of patients taking failing antiretroviral (ARV) regimens. We intend this article to provide a practical guide to help clinicians understand and manage ARV drug resistance in an African context.

ARV resistance is a rapidly evolving field, requiring expertise in dealing with a wide range of situations. Much of the information we have on ARV resistance is from populations in the developed world where clade B is the biggest problem, while in most of Africa clade C is the commonest infection.

Southern Africa is faced with the daunting prospect of putting several hundred thousand people on ARV therapy (ART) in the next few years.[1] ART is the only effective option available to people with advanced HIV disease, and is remarkably effective in improving quality of life, increasing lifespan, dramatically decreasing the burden of opportunistic disease, and returning people to productive life.[2]

The levels of adherence demanded by ARV regimens are extremely high relative to any other chronic disease. The South African government's Comprehensive Care for HIV/AIDS in the Public Health Sector[3,4] programme has a 'second-line' ARV regimen (Fig. 1), specifically as a safety net for people failing the first-line regimen. Other countries do not have this luxury. The SA second-line regimen is more difficult to take, has greater toxicity, and is more expensive than the first-line treatment.

ARV resistance often compromises future treatment options. The choice of regimens in the SA programme maximises the use of available drugs in this country.

Our experience of private practitioners in South Africa is that they use a range of drug regimens other than those recommended in the government guidelines. There is no effective mechanism to enforce use of the government's recommended drug regimens, but we feel that they are the most rational use of drugs currently available in SA and that deviation from guidelines in routine use should be discouraged, unless alternative options exist. AZT/3TC is still a popular combination, and there are excellent data to support its use as the nucleoside reverse transcriptase inhibitor (NRTI) backbone in first-line therapy, but the alternatives available when resistance to this option develops (i.e. d4T with ddI) are very toxic. In other countries, alternative regimens may be more appropriate.

While we have focused on adult ARV choices in this article, the same principles generally hold for children, although choice of drugs is currently different. Again, we recommend the use of the SA guidelines, published in the November 2005 *Journal.*

CLINICIAN'S GUIDE TO PATHOGENESIS OF ARV RESISTANCE

The HIV reverse transcriptase enzyme lacks a proof-reading capability. This is the key to both the virus's rapid evolution, causing highly effective and continued evasion of the immune system, and the rapid development of drug resistance.

Depending on the stage of the disease, up to 10 billion HIV virions are produced in HIV-positive people every day. Each virion has a half-life of about 30 minutes. The viral swarm consumes huge numbers of lymphocytes every day.

The genetic strand that codes for the virus is 10 000 nucleic acid base pairs long, and a mistake occurs, on average, approximately every 10 000 translations. The absence of the

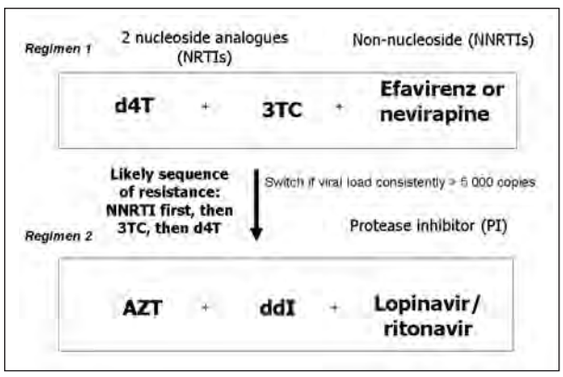


Fig. 1. South African government 2004 recommendation for sequencing of ARVs; nevirapine use for women wanting/at risk of pregnancy.

proof-reading function means that, on average, there is a nucleic acid mutation in every single copy of the virus. It is estimated that every known mutation occurs 10 000 to 100 000 times in every person with untreated HIV every single day.

Mutation rates accelerate when there is accelerated viral replication – i.e. the faster the virus is produced (e.g. when someone has tuberculosis), the more mistakes are made. Some mutations are useful to the virus, allowing it to duck and dive away from the antiviral properties of the immune system and ARV drugs. Other mutations (in fact, most) are harmful, making it more susceptible to both the immune system and/or ARVs. These weakened forms are rapidly outcompeted, as the fittest version exercises its replicative advantage and outgrows the competitors.

Of course, some progeny will have no mutations while others will have multiple changes, but the massive replication means that selection for more virulent strains is inevitable: what has been termed a 'predetermined agenda'. This leads to the development of quasispecies, HIV 'gangs' competing against each other for the same turf in the human host. The term 'wild type' refers to the most effective gang that exists in the absence of ARVs and the absence of significant ARV mutations. 'Fitness' reflects how much replicative ability the virus has. The 'fittest' wild type will prevail, unless something comes along that changes the natural order of things – like an ARV drug.

It has been estimated that untreated HIV-positive people have every known ARV resistance mutation somewhere in their bodies at any given moment, despite *never having been exposed to ARVs!* This occurs by pure chance – the 'predetermined agenda'. However, in the absence of ARV selection pressure, these quasispecies cannot out-compete the wild-type strain.

WHAT IS ARCHIVING?

At each step, replicatively effective viral DNA is 'archived', or integrated into non-replicating or slowly replicating cells throughout the body (e.g. memory T cells and macrophages). This means that the body houses a memory bank of all effective virus quasispecies it has witnessed within its tissues. If a potent selection pressure inhibits the 'wild-type' virus, and the 'archived drug-resistant virus' starts to replicate, it can rapidly spread and become the predominant quasispecies. It seems that resistance mutations to some drugs are 'remembered' (archived) in the host human DNA better than others, but, disastrously, ARV drug resistance can be uncovered after many years of effective viral suppression.

So why do the ARVs work at all, given all this mutagenic ability? Many mutations (but not all) interfere with the virus's replicative and infectious ability. A virus with several mutations to exposed drugs may be so crippled that it is unable to be viable (Fig. 2).

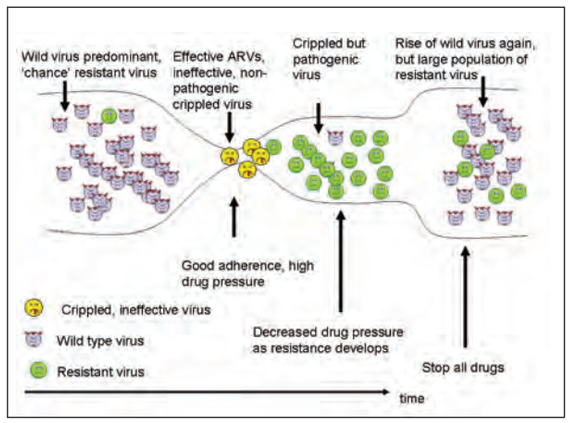


Fig. 2. The evolution of HIV resistance.

IS DRUG RESISTANCE LIKELY TO BE A MASS PROBLEM IN AFRICA?

Probably, but mathematical modelling suggests not for at least a decade, and that the impact may be limited.[5,6] The spectre of some sort of a multidrug-resistant, super-infectious, super-virulent super-virus is the stuff of newspaper headlines, but has never been reliably identified. In Europe and America, as treatment evolved during the late 1980s and early 1990s, ARVs were initially used as monotherapy, then as dual therapy, resulting in a high background prevalence of NRTI resistance in treatment-experienced patients. More recently, even some triple combinations (e.g. AZT/3TC/ABC, Trizivir) have been shown to be associated with a high likelihood of treatment failure and development of resistance. Along with this, patients on ARVs in developed countries have a high rate of non-adherence, making the general community resistance to everyday commonly used ARVs a big problem. Interestingly, it seems that community resistance to ARVs in developed countries may be on the wane – possibly because the use of more potent cocktails decreases the transmissibility of drug-resistant virus.[7,8] However, on deeper analysis of the patterns of transmitted resistance it appears that non-nucleoside reverse transcriptase inhibitor (NRTI) community resistance is steadily increasing, while other class mutations are decreasing.

However, individual patients with drug-resistant virus are already cropping up in South Africa, and several case and anecdotal reports have emerged of people with mutations associated with severe drug resistance.[9,10] These patients are difficult and expensive to manage. It is every clinician's responsibility to reduce the community prevalence of resistance by looking after their patients responsibly and carefully, checking adherence at every visit, avoiding drugs that interfere with ARV metabolism, and checking the viral load regularly. This is the same model as for TB treatment – multidrug-resistant (MDR) TB is a product of poor adherence and poor patient follow-up by the health services. HIV evolves resistance much faster than TB, so poor management is likely to have rapid consequences.

In future, as is the case in developed countries, we may begin recommending routine resistance testing of infected people. At present, this is probably unnecessary in the vast majority of patients.

KNOWING THE ENEMY: SIGNATURE MUTATIONS

HIV specialists, like other medical professionals, are addicted to deep and impenetrable jargon. There are over 200 known resistance mutations, and new ones are being described all the time. However, there is little point in remembering the mutations. It is necessary to understand the drugs you use, and then how to spot and deal with resistance.

We believe that the average clinician needs to know how quickly resistance develops to the ARVs they use regularly, and the clinical implications of that resistance. For the sake of completeness, we will cover the more common resistance mutations, and explain how the nomenclature evolved.

The enzyme reverse transcriptase transcribes viral RNA to DNA. The reverse transcriptase gene is 560 amino acids long. A common resistance mutation to the drug 3TC is at the 184 location, where valine replaces methionine. This is called M184V (methionine is the 'normal' nucleic acid replaced at position 184 with valine). Simlarly, K103N is a mutation to NNRTIs in adults, with lysine (K) replaced at position 103 with asparagine (N). The first letter is sometimes left off, as shorthand – i.e. 184V, 103N.

Proteases assemble the virus in the cytoplasm. The protease gene is only 99 amino acids long, and a D30N would imply aspartic acid (D) is replaced with asparagine (N) at position 30. This is a common mutation associated with the protease inhibitor nelfinavir.

The term 'drug resistance' as a blanket term is fuzzy – it may be total or partial, depending on the drug, and resistance to one drug may even confer increased susceptibility to another. The nomenclature is further confused by terms such as 'major' and 'minor' mutations, or 'primary' and 'secondary' mutations, muddled even further by the fact that the field is evolving so fast that new insights often make these terms archaic before they enter common use. To make life even more difficult, different clades seem to have different patterns in the development of resistance. Luckily, the resistance patterns tend to consign themselves to a distinct class, although some subtle overlaps are starting to emerge. These are not yet of clinical significance.

Three classes of drugs are currently available in southern Africa.

1. THE NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS

Nevirapine and efavirenz are widely used in southern Africa and throughout the world. The drug binds directly to the reverse transcriptase enzyme, rendering it ineffective. The commonest mutation in the reverse transcriptase gene stabilises the site that binds the enzyme, making it less able to bind effectively. New NNRTI drugs in development are able to bind despite this mutation.

Resistance to this class is the easiest to understand – resistance occurs rapidly (often after a single dose if used alone). There is complete class resistance, so complete resistance to efavirenz means that nevirapine is useless, and vice versa.

There are several NNRTI resistance mutations, almost all contributing profound resistance throughout the class – the commonest is K103H, and another is Y181C. A distinct mutation has been described to clade C virus (V106M) which is the predominant clade in SA, and this resistance mutation has been described in this the country.[11,12] Only one point mutation is necessary to cause complete resistance to both efavirenz and nevirapine. The resistance mutations unfortunately do not seem to alter the virus's replicative ability, and transmission of resistance from one person to another is of major concern – the mutation does not affect fitness.

The use of nevirapine for the prevention of mother-to-child transmission deserves special mention in southern Africa. Large numbers of women are being exposed to this treatment, which involves a single dose of nevirapine to the mother during labour, and a postpartum dose to the neonate. It is remarkably effective and safe in preventing transmission to unborn children, but high rates of nevirapine resistance mutations have been described months after administration.[13,14] This makes sense, as only a single mutation confers resistance, and the drug has a very long half-life, meaning that the virus is exposed to it for a prolonged period (resulting in several days of nevirapine monotherapy), increasing the period of selection pressure. A trial done in Thailand suggests that women with mutation may be at high risk of failing a subsequent NNRTI-based regimen.[15] However, the evidence is not completely clear-cut, and the World Health Organization and local experts are currently reviewing the guidelines and evidence as it emerges. Until clear guidelines are available, it is probably acceptable to treat women treated with single-dose nevirapine and subsequently with regimen 1a as if they had not been exposed.

In summary: NNRTI resistance is of major clinical significance – it is easy to mess it up; mess it up, and you confine this very useful class to the dustbin of options.

2. NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS – THESE DRUGS MIMIC DNA'S BUILDING BLOCKS

d4T and 3TC are part of the South African Department of Health (DoH) first-line regimen, AZT and ddI are part of the DoH's second-line regimen (see Fig. 1). Other drugs used in SA include abacavir. Tenofovir (TDF), a new variation in the NtRTI class with a unique resistance profile, is eagerly anticipated as a once-daily and safe alternative to d4T. TDF (a nucleotide RTI) shares resistance mutations with ddI and ABC (K65R), and is rendered ineffective by NRTI-class resistance mutations.

Resistance to NRTIs is far more complex. There is cross-resistance between some drugs in this class, and none for others. Resistance mutations occur on the reverse transcriptase enzyme. These are often far from the area coding for the active site, but induce conformational changes that have indirect changes at the active site making it more 'discerning' towards NRTIs, or facilitate the removal of the drug from the binding site.

The easiest to understand is resistance to 3TC. A single mutation, the famous M184V mutation, confers complete resistance to 3TC, similar to the way a single mutation confers complete resistance to the NNRTIs. The 184 mutation can also occur in the presence of emtricitabine (FTC, a new NRTI, not yet available in SA but very similar to 3TC), abacavir, and occasionally ddI. Its impact on ddI and abacavir is far less profound than on 3TC. Also similar to NNRTIs, resistance occurs rapidly, although it tends to occur at a slightly slower pace, usually within weeks of exposure to 3TC in the presence of a detectable viral load.

There is one potentially important difference to the NNRTIs: the M184V mutation seems to deeply affect the pathogenicity and possibly the transmission potential of the virus. There is interest in keeping people on 3TC even if they are resistant to it, in salvage therapy, usually after failure of two regimens. The M184V virus that one sees in the blood of patients on failing 3TC-containing regimens is less 'fit', and more easily controlled by the immune system and subsequent drug treatments. While the M184V mutation makes the drug slightly less effective than abacavir and ddI, it seems to 'sensitise' HIV to AZT, ddT and tenofovir. Increasingly, experienced clinicians are using it as a viral 'crippler', adding a triple cocktail on top of the 3TC therapy. Evidence for this is sparse at present, but 3TC is regarded as a safe drug, and adding it on seems to make sense. However, until clearer guidelines are available it should only be done in consultation with an expert.

The situation with the 'thymidine analogues' AZT and d4T is more complex. Both drugs have cross-resistance, and both need several mutations before clinically important resistance occurs. This often takes several months of unopposed non-suppressive treatment, and resistance therefore accumulates serially. Resistance mutations to these are known snappily as TAMs (or, less snappily, as thymidine analogue mutations). Examples include the bewildering array of 41L, 67N, 70R, 210W, 215 Y/F and 219Q/E. 'TAM' is probably a misnomer, as these mutations affect more than d4T and AZT, and may decrease the efficacy of other nucleosides including didanosine, tenofovir and abacavir, although other NRTI mutations are necessary. The development of mutations at area 69 (most commonly T69S) confers variable low-level drug resistance against almost all nucleosides, but this seems to increase the impact of subsequent mutations. Interestingly, TAMs seem to have no effect on the efficacy of 3TC, and the combination of AZT, 3TC and a potent third drug like Kaletra appears to be very effective even when several TAMs are present.

So called 'non-thymidine' mutations include K65R, which is selected by tenofovir and reduces susceptibility to all NRTIs except AZT, where it improves sensitivity; and Q151M and L74V, which decrease the efficacy of a range of NRTIs.

Didanosine (ddI) has a high resistance barrier, requiring serial mutations before it loses efficacy, and tends to select mainly for L74V. Abacavir is a 'dirty' drug, as the resistance mutations to it are very difficult to predict clinically. Multiple TAMs and the K65R mutation, however, are likely to decrease the effectiveness of abacavir.

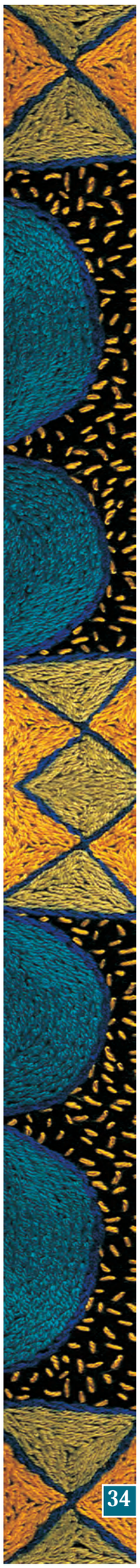
In summary: Unlike the NNRTIs, resistance is not generally catastrophic. However, it is much more complex, and approaches to resistance are steadily becoming more sophisticated, dealing with issues of cross-resistance, partial 'revertants' and hypersusceptibility.

3. PROTEASE INHIBITORS (PIs)

Generally the PIs require multiple mutations to acquire resistance. They are the 'tough guys' of the ARV revolution, but some are tougher than others.

'Boosting' is the term used to describe increasing the level of PIs by adding ritonavir to the mix. This dramatically increases the blood concentrations, and makes development of resistance much more difficult. The ritonavir role is pharmacological only – it has minimal ARV activity at this very low dose. Boosting seems to protect against the development of multiple PI mutations. Interestingly, this strategy also seems to protect other classes of drugs, especially the nucleosides, from developing resistance. Nelfinavir is the only PI not 'boostable' – the addition of ritonavir only marginally increases the blood levels.

New mutations to PIs are being described, and clinicians have begun classing mutations into 'major' and 'minor' – based on how much the mutation actually stops the action of the drug. As mentioned above, this nomenclature is challenged by the new information on these mutations. It is often possible to



change one PI for another, much like the nucleoside analogues, although resistance testing makes this less like guesswork. Kaletra (lopinavir/ritonavir), used in the South African rollout, appears to need more than 6 mutations to acquire resistance, while nelfinavir usually requires only 1 to reduce its efficacy 5-fold, and 2 to reduce it 50-fold. Some PIs need specific mutations, but the common mutations occur at positions 82, 84 and 90.

A new PI, atazanavir, appears to induce a mutation (150L) that actually *increases* susceptibility to other PIs. This has also been described with saquinavir and amprenavir. Whether this is clinically useful is still up for debate.

So what to do? There is lots of clinical debate about which PI is best to start with, and which to use next. It appears that we may have third- and fourth-line choices now, and the old 'one strike and you're out' has evolved into a place where it seems that certain PIs may even be recycled, despite archiving, a theory considered heresy a few short years ago. New PIs are on the horizon, with new resistance profiles. If these drugs were less toxic, the future would seem rosy.

Bottom line: In South Africa the national guidelines use Kaletra, the ARV equivalent of the Great Wall of China. Failing this drug is very difficult, but is possible (the first patient to fail it was described from SA![9]). Other PIs can then be used in its place, although these do not form part of the national guidelines. Generally, the world is moving away from indinavir and saquinavir, because of toxicity and because the resistance profile is 'dirty', influencing the choice of future regimens.

Once the first PI regimen has failed, it is not recommended that nelfinavir, unboosted atazanavir or unboosted amprenavir is used, as cross-mutations to these make them less likely to succeed. However, 'sequential' PIs can be used. Atazanavir and amprenavir will probably soon become available in SA. Experts are increasingly using 'double-boosted' PIs, sneakily adding two PIs to a single dose of rintonavir – but it is not clear which two PIs to add to the ritonavir, although lopinavir and saquinavir are popular.

In summary: We feel NNRTIs are more appropriate than PIs initially, for reasons of ease of use, toxicity and cost. We advocate lopinavir/ritonavir as the first PI you use, and then suggest you consult expert help for the next choice. Let's hope that by then we'll have sorted out the bewildering array of options available.

ROLE OF DRUG INTERACTIONS AND DRUG RESISTANCE

Drug interactions may decrease the effective dose of certain ARVs, leading to resistance. TB drug co-administration is common, as patients enter the programme from TB programmes, or get placed on rifampicin-containing regimens after developing immune reconstitution syndromes. Rifampicin, NNRTIs and PIs all affect CYP 3A4 and therefore can decrease the plasma levels. Rifampicin administration increases efavirenz and nevirapine metabolism and theoretically could drop levels leading to potential dual therapy. Some authorities recommend increasing the dose of efavirenz in the presence of rifampicin, but evidence suggests that this is unnecessary. The current South African guidelines suggest no dose adjustment of efavirenz, and our anecdotal experience is that this is correct. Similar concerns with Kaletra exist, and here the SA guidelines suggest adding a whopping 300 mg ritonavir bd to the standard Kaletra dose, to counter the accelerated metabolism.[2,3,16-19]

IS DRUG RESISTANCE TESTING AN OPTION?

The answer to this is a highly qualified yes. Genotypic resistance testing is available through a large number of laboratories in SA, but not in the DoH rollout, as the benefit is not felt to justify the cost.

Genotype testing involves the extraction and amplification of the predominant viral genome in the blood, and seeing if known genetic mutations to ARVs are present. The weakness of the testing is that it does not detect archived virus, may miss small populations of resistant virus in the blood, only detects known resistance mutations, takes time and is expensive. The test should ideally be done while still on the 'failing' regimen, otherwise 'wild' non-resistant virus may obscure the smaller population of resistant virus. There must be enough virus to do the test (at least 1 000 copies/ml). Results have to be interpreted against an accurate history of ARV use, and must be interpreted by an expert in the field. Resistance testing is useful on a population basis, for the surveillance of prevalent drug resistance, but our experience is that most of these tests, when ordered by non-experts, are a waste of money and time. In the hands of experts, they may add to the chance of success of a subsequent 'best guess' ARV regimen.

The rule is: Do not order a resistance test *unless* you have spoken to an expert.

Phenotypic resistance testing is more analogous to a conventional microscopy, culture and sensitivity (MC&S) most clinicians are very familiar with, with the virus grown against different types and concentrations of antiretrovirals. Unfortunately, it is expensive and currently only available in research laboratories in developed countries. 'Virtual phenotyping' uses genotyping and match genotypes to brown phenotypes and ARV history to predict overall resistance patterns, and may hold promise for improved use of genotype testing in the future.

DOES STOPPING ARVs SUDDENLY CAUSE RESISTANCE?

This is a thorny issue. The commonest reason for stopping treatment is possible toxicity, or running out of funding for treatment.

Consider a patient on d4T, 3TC and efavirenz (Fig. 3): If you suddenly stop treatment, the level of d4T drops very soon, as it has a short half-life, leaving the patient effectively on 3TC and efavirenz (dual therapy). Then the levels of 3TC drop, and the only effective drug left is efavirenz. Efavirenz has a half-life that lasts days and occasionally weeks, and has a very low resistance barrier, so it makes sense that resistance will develop quickly. Preliminary studies have demonstrated resistance, but it is unclear whether this is clinically important.

Many clinicians now 'cover the tail' – they continue the drugs with high resistance barriers to cover the vulnerable NNRTIs (see Fig. 4). No one is sure how long we should continue these (although many of us use a week), or even if it is effective. If the drug level of efavirenz dropped suddenly, and you're left with just d4T and 3TC for a few days, significant resistance is unlikely. The difficulty with this is that if you are stopping due to NRTI toxicity, e.g.pancreatitis, you would need to stop the NRTIs at the same time.

In many situations it is not practical to cover the tail, especially if there is severe illness where it is unclear whether it is a drug reaction or immune reconstitution. In these cases, rather stop all the drugs, and pick up the resistance pieces once the crisis is over.

CAN I DELIBERATELY CRIPPLE THE VIRUS?

The 3TC mutation appears to decrease viral fitness, and may even make other drugs more potent, especially AZT, d4T and tenofovir. If there is existing 3TC resistance, some clinicians (including ourselves) continue 3TC, adding it to the next regimen as a way of decreasing fitness. Do *not* add 3TC as a viral crippler if there is no resistance to it – use it as a normal ARV!

HOW LONG DOES RESISTANCE PERSIST FOR?

Resistance mutations acquired sexually from someone else (i.e. passed directly on) seem to persist for much longer than those found when selected by the virus. Resistance usually 'disappears' slowly from the bloodstream, as wild or fitter virus comes back in the absence of ARVs. Some mutations disappear before others – the 3TC mutation M184V disappears within a few weeks, while others can persist for years.

WHAT ABOUT DOING DRUG LEVELS?

Therapeutic drug monitoring (TDM) is not yet generally available to southern African clinicians. It seems likely that it will be very useful in the future, especially in dealing with complex drug interactions, side-effects, or difficult physiological conditions (such as pregnancy), and where genetic or other factors impact on plasma levels. In the case of PIs in particular, this may make life significantly easier. Testing is not available for the NRTIs. Watch this space for future recommendations regarding TDM.

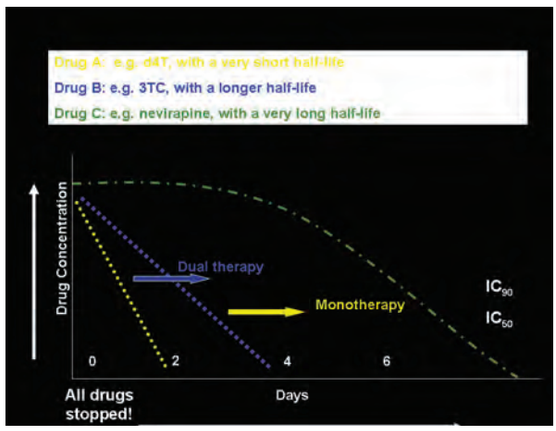


Fig. 3. Different half-lives mean that triple therapy can evolve into dual and monotherapy ...

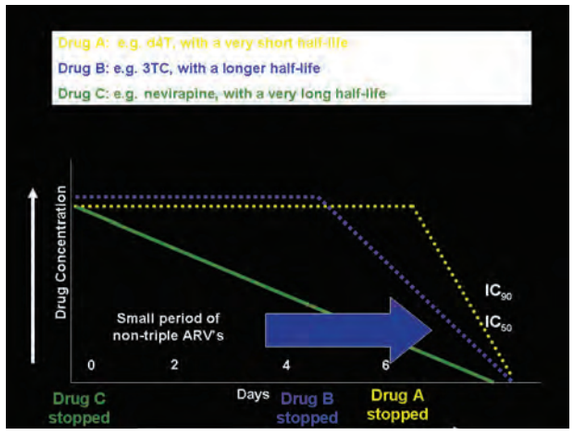


Fig. 4. Cover the tail! How to stop drugs with different half lives ...

A PRACTICAL APPROACH TO A PATIENT FAILING THEIR FIRST REGIMEN

Questions to ask when faced with a patient on ARVs and possible drug resistance ...

1. HOW DO YOU KNOW THAT THE PERSON IS RESISTANT?

A viral load persistently detectable on *stable* treatment generally equates to resistance. Remember that it takes 3 - 4 months for the viral load to 'decay' (although an effective regimen should cause a 1.5 $\log_{10}$ drop in viral load after 4 weeks).

It is generally wise to confirm the elevated viral load, by repeating the test. Many people have viral 'blips' or sudden increases for some reason, and occasionally the test can yield a falsely elevated level. Confirm the increase before substituting the regimen.

If someone has a detectable viral load, and you know or suspect that the patient has interrupted therapy, or is not completely adherent, or has a drug interaction, or is inadequately dosed, intensify adherence support, sort out the problem and measure the viral load a few weeks later. If it

becomes undetectable, you have probably avoided an unnecessary drug substitution.

However, a persistently raised viral load usually means drug resistance and you need to consider a change. In the SA programme, a persistently raised viral load above 5 000 copies (preferably measured on two occasions 4 weeks apart) should signal the need for a change.

2. WHAT CLASSES OF DRUGS IS THE PERSON ON?

Resistance is fairly predictable (see Fig. 3). NNRTIs are very vulnerable, and a single mutation confers complete resistance. This is usually the first class to show resistance.

Next is usually 3TC, which is also vulnerable to a single mutation.

The other drugs (nucleosides and PIs) generally follow, albeit slowly. It usually takes months to develop resistance to these. Resistance testing is useful to show whether there is actually resistance to NNRTIs and 3TC, and how much resistance there is to the other nucleosides and PIs, if any.

3. HOW LONG HAS THE PATIENT BEEN ON THIS REGIMEN?

If only a few months, it is unlikely that significant resistance will have accumulated to anything other than the NNRTI and 3TC. However, if a patient has been left on a failing regimen for many months, the other drugs in the regimen are increasingly likely to have resistance mutations develop against them.

4. WHAT ARE YOUR OPTIONS NEXT?

If you have resistance testing results and it has been done properly, consult with an expert.

If resistance testing is not an option:

- Consider using a boosted PI. The resistance barrier in this class is significant.
- Consider adding 3TC as a 'crippler' – but only if you are sure you have pre-existing viral resistance.
- Consider new drugs – consult with an expert, as a host of new drugs are eagerly awaited in the next few years. Or ask around if a clinical trial is being conducted.
- Consider a treatment interruption. In some cases, interrupting therapy seems to allow for some resistance to wane, and for future options to be more effective. Again, get expert help – consider the indication for the original decision to start ARVs; the risk of illness and decline in CD4 must be weighed carefully against the benefit.
- Finally, consider just leaving them on the regimen – if there are no other options. It is clear that patients with resistant virus left on their failing regimens live longer and better.[20,21]

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THE 12 COMMANDMENTS OF PREVENTING ARV RESISTANCE

1. Adherence is next to godliness! Take the needed time to make the patient understand how important adherence is.
2. Thou shalt not kill! Do not simply guess at the next regimen for your patient – get expert help. Our patients have limited options in Africa.
3. Do not be a deviant! Have a VERY good reason to digress from the DoH's ARV guidelines.
4. The only good viral load is a dead one! Anything detectable after 3 – 4 months of treatment means resistance is present or developing. Do something.
5. Thou shalt not order a resistance test without first asking an expert!
6. Thou shalt not covet other ARVs! Do not use drugs you are not familiar with.
7. Smite other clinicians who do not listen to these commandments! Or at least tell them to be more responsible.
8. Consider covering thy tail! Remember that NNRTIs hang around for ages.
9. Respect the struggle! Lifelong adherence to ARVs is tough, and is a daily reminder to patients having to live with a highly stigmatised disease. Discuss adherence at every consultation.
10. Resistance does not always equal clinical outcomes! Resistance does not always mean virological (VL detectable) failure. Virological failure does not always equal immunological (CD4 decreasing) failure. And immunological failure does not always equal clinical failure. Do not give up – it is rare that patients run out of ARV options even in the face of significant resistance.
11. Never add a single drug to a failing regimen! It may be the equivalent of monotherapy if there is resistance to the other drugs.
12. Do not give up hope for your patient!

SOUTHERN AFRICAN HIV CLINICIANS SOCIETY

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Aspen Pharmacare pledges R 100 000.00 Annual Unconditional Educational Grant to Southern African HIV Clinicians Society

Dr. Francois Venter, President of the Southern African HIV Clinicians Society gratefully received the 2006 Unconditional Education Grant from Aspen Pharmacare. He thanked Aspen Pharmacare profusely for the ongoing funding which allows doctors who would not otherwise be able to attend conferences, to do so.

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Aspen Pharmacare s Mr. Gavin Wiggill and Mr Jackie Tau hand over the cheque for R 100 000.00 to a delighted Dr. Francois Venter

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HIV AND END-STAGE RENAL DISEASE: PRACTICAL ISSUES IN MANAGEMENT

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According to UNAIDS data there are 40 million HIV-infected people around the globe. An uncommon complication of HIV is HIV-associated nephropathy (HIVAN), and this condition is expected to be one of the leading causes of end-stage kidney disease (EKD) in black men in the new millennium. Patients present with an immune complex glomerulopathy and focal segmental glomerulosclerosis together with proteinuria and haematuria and occasionally severe hypertension. Peripheral oedema is unusual. In the era before antiretroviral therapy (ART) the median survival in the HIV-infected population on dialysis was 10 months. However, since the introduction of highly active antiretroviral therapy (HAART) and optimal prevention of opportunistic infections, a life expectancy of 10 - 20 years can be expected. Unfortunately patients infected with HIV are often excluded from renal replacement therapy (RRT) programmes despite such encouraging outcomes and despite the fact that the outcome of renal transplantation in HIV patients is comparable to that in HIV-negative recipients at 1-year follow-up in experienced centres. In the South African context HIV/AIDS has an alarming prevalence, although dialysis and transplantation are offered only to very few and often only in the acute state. In the light of the new data, HIV seropositivity (especially when the patient is receiving HAART) needs to be reconsidered as an absolute contraindication to renal replacement.

EPIDEMIOLOGY AND PATHOLOGY

In South Africa a national community-based survey suggests that HIV prevalence in the general population is close to 12% (12.8% in females and 9.5% in males).[1] Equally alarming is the finding that an estimated 15.7% of health workers employed in the public and private health facilities located in four South African provinces are infected with HIV/AIDS.[2] Chronic kidney disease develops in 2 - 10% of patients and risk factors include African descent, male gender, and a concomitant diagnosis of diabetes or hypertension and proteinuria.[3] The development of HIVAN has definitively been linked to renal cellular infection and focal segmental glomerulosclerosis appears to be the commonest glomerular pathology. The fact that the disease typically affects men of African descent has obvious consequences in the South African context.

PRE-DIALYSIS

There appears to be a high prevalence of proteinuria on the first urine analysis obtained after HIV documentation.[4] Early treatment with HAART and angiotensin-converting enzyme (ACE) inhibition may offer long-term renal survival benefits in HIVAN, and in addition some clinicians have used low-dose steroids.

RENAL REPLACEMENT THERAPY

Despite rates of EKD in the general population in South Africa estimated to be about 400 per million population (pmp), only 99 pmp receive RRT.[5] For this reason patients suffering from HIV and EKD are excluded from long-term dialysis programmes. Such exclusions may be based on historical grounds, as previously survival was poor, and on fear of cross-infection to other dialysis patients and dialysis staff. More recently the survival of HIV-positive patients has improved and is often equal to or better than those not infected with HIV.[6]

HAEMODIALYSIS

The risk of nosocomial HIV infection to health workers in the dialysis setting is a concern owing to the nature of needle access for haemodialysis (HD). The risk of infection from percutaneous exposure to infected blood is 0.3%.

Initial misinformation and panic regarding acquisition of HIV created great concern, and extreme precautions against the infection were taken. Dialysis units treating infected patients often resembled a set from a science fiction movie, with staff wearing caps, gowns, masks and booties and most patients being strictly isolated with their own dedicated dialysis machines. Some shared machines with patients infected with highly infectious hepatitis B! The more modern approach proposed by the Centers for Disease Control (CDC) in the USA stresses the adoption of universal blood and body fluid precautions, standard disinfection and sterilisation strategies during dialysis, and careful control of dialyser re-use where practised. Dialysis machines should not be shared between patients with HIV and those infected with hepatitis B, and isolation of HIV-infected patients and dedicated machine use is currently not recommended by the CDC or the National Kidney Foundation (NKF) task force on dialysis.

In the pre-HAART era survival of HIV-infected patients was dismal to the point at which it was an ethical dilemma whether chronic dialysis should be offered to these patients. However, with the use of HAART the survival of HIV-infected patients on dialysis has improved considerably. Importantly however, it has been suggested that HD may activate HIV replication, although considering the potent antiretroviral (ARV) activity of the newer HIV drugs activation of HIV seems unlikely.

PERITONEAL DIALYSIS

Theoretically peritoneal dialysis (PD) poses less risk than HD to dialysis staff and other patients as PD fluid is less infectious than blood. The glucose load provided by PD fluid affords the patient an adequate caloric load, although protein losses may actually worsen the patient's nutritional status. Survival rates are comparable to those for patients receiving HD. Controversy abounds regarding a supposed increased risk of peritonitis, especially when the patient is in an immunocompromised state. Studies have shown increased rates of *Pseudomonas* and fungal infections.[6] Once the expected immune reconstitution on HAART occurs, the risk of peritonitis falls to that in patients not infected with HIV. Adequate disinfection protocols are essential when performing PD as both HIV p24 antigen and HIV antibodies have been found in PD fluid.

Both HD and PD are effective modalities of RRT in the HIV-infected EKD patient. The choice of modality should depend on the individual's lifestyle and availability of adequate family support and medical expertise. A prerequisite is that such patients should receive optimal ART.

HIV seropositivity should not be a negative dialysis criterion. Patients with HIVAN and EKD should be allowed to choose a specific dialysis modality, because it is not a factor in predicting survival.[7] When progression to kidney failure is suspected timely fashioning of an arteriovenous fistula should be considered, as well as the placement of a PD catheter. Temporary HD lines are best avoided in those patients with EKD as long-term vascular access may often be compromised by such catheters.

TRANSPLANTATION

The arguments in favour of transplantation for HIV-infected patients have gained a new impetus with improvement in survival on HAART. In the South African context experience with transplantation in HIV-positive patients is limited. Major issues in this regard include:

- false-positive tests for HIV pre- and post-transplantation
- transmission of HIV infection through the allograft
- outcomes of HIV-positive patients who undergo transplants, and
- acquisition of HIV-infection following transplantation.

Interestingly, immunosuppressive agents such as cyclosporin and tacrolimus may retard replication of HIV virus, and mycophenolate mofetil may potentiate the ARV effect of commonly used HIV drugs.[9]

GENERAL PATIENT MANAGEMENT

ANAEMIA

Anaemia is common in HIV-infected patients with renal disease, and overall anaemia is the commonest haematological abnormality in HIV-infected patients. Mean haematocrit levels in patients with HIVAN are lower than in other patients with end-stage renal disease (ESRD) starting dialysis. HIV infections may exacerbate anaemia in patients with kidney disease by direct effects of HIV infection on erythropoiesis, opportunistic infections, ARV drugs, and other rare mechanisms such as thrombotic microangiopathies. Such anaemia is independent of other factors associated with shorter survival and it should be managed as aggressively, e.g. with recombinant human erythropoietin (EPO), which is utilised for any patient with EKD. HIV-positive patients often require higher doses of EPO to maintain adequate haemoglobin levels. Although rare, parvovirus B19 infection should be suspected if anaemia in the HIV-infected patient does not respond to EPO and other causes have been ruled out. Iron is essential for haemoglobin formation and iron status should be monitored and corrected accordingly by the percent transferrin saturation and serum ferritin levels. In this situation it is important to realise that ferritin levels are often elevated in patients with HIV infection as a marker of inflammation, and high iron stores may also adversely influence outcome in HIV-infected patients. Some studies have shown that oxidative stress and iron may activate HIV-1, and when intravenous administration of iron is carried out, viral loads need to be monitored.

VACCINATION

The immunosuppression that results from HIV infection and uraemia is likely to lead to suboptimal response to vaccination. Immunisation for hepatitis B in HIV-infected EKD patients is important because not only does hepatitis B virus infection occur more frequently in HIV-positive subjects, but these patients also are more likely to develop chronic hepatitis B infection. Unfortunately, however, antibody response to hepatitis vaccination is impaired in HIV-infected patients, only half of whom develop a protective antibody response.[8]

There is a concern regarding the drug-drug interactions between protease inhibitors and calcineurin inhibitors, and vigilant drug level monitoring is imperative.[10] Although relatively few patients with HIV currently undergo organ transplantation, patient and graft survival are comparable to United Network for Organ Sharing (UNOS) figures at 1 year of follow-up. Furthermore, there is no evidence of progression of HIV disease, and as experience grows in this field asymptomatic HIV-infected patients with ESRD may be offered this most optimal of renal replacement therapies.

Adequate and accurate testing of any cadaveric or living allograft for HIV infection, especially in high-risk populations,

reduces the risk of transmission to the recipient although such infections do occur.

An adequately functioning allograft restores sexual and reproductive function in the recipient of any kidney allograft, and in parts of the world where the prevalence of HIV is high (such as in South Africa) HIV infection following transplantation is a real concern.[11]

ISSUES RELATED TO HAART

The aim of ART in EKD patients with HIV should be to reduce the viral load to undetectable levels and to prevent opportunistic infections. With the use of HAART, improved prophylaxis and treatment of opportunistic infections there has been a dramatic improvement in survival of HIV-infected patients, although such therapy is often under-utilised in HIV-infected patients with EKD.[10]

There are three main groups of ARV drugs, nucleoside and non-nucleoside reverse transcriptase inhibitors (NRTIs and NNRTIs) and protease inhibitors (PIs). In most patients a combination of either two NRTIs with a PI or two NRTIs plus one NNRTI are used. NRTIs used in HIV therapy are primarily excreted by the kidneys, so the dose administered to EKD patients is 30 - 50% of the normal dose for various drugs (see Table I). In addition, on dialysis days the NRTIs should be given after dialysis. Abacavir is the only NRTI the absorption, elimination and distribution phases of which are not altered by renal insufficiency and which does not need dose adjustment in patients with ESRD. Since abacavir is mainly metabolised in the liver, the fraction removed during dialysis is not clinically significant, and it can be administered at any time on dialysis days. NNRTIs and PIs are mainly metabolised in the liver by cytochrome P_{450} isoenzymes, and do not need dose adjustments in patients with ESRD. NNRTIs should be administered after haemodialysis to minimise loss during dialysis. In contrast, PIs can be administered regardless of the dialysis schedule. Table I details dosage adjustments of ARV agents required in patients with kidney insufficiency.[12]

Use of ARV drugs is a double-edged sword in that despite their positive antiviral properties their use results in a number of renal abnormalities. Table II details such effects.[13]

TABLE I. ORAL DOSAGE RECOMMENDATIONS FOR ANTIRETROVIRAL DRUGS IN HEMODIALYSED PATIENTS[12]

Drug	Normal dosage	Haemodialysed patients
NRTIs		
Zidovudine*	200 mg tds	100 mg tds
Didanosine*	200 mg bd	200 mg daily
Zalcitabine*	0.75 mg tds	0.75 mg qd
Stavudine*	40 mg bd	40 mg daily
Lamivudine*	150 mg bd	150 mg stat then 250 mg q 24 h
Abacavir*	600 mg bd	Normal dosage
NNRTIs		
Nevirapine*	200 mg daily for 14 days then 200 mg bd	Normal dosage
Delavirdine*	400 mg tds	NA
Efavirenz	600 mg daily	Normal dosage
PIs		
Saquinavir†	600 mg tds	Normal dosage
Ritonavir	600 mg bd	Normal dosage
Indinavir	800 mg bd	Normal dosage
Nelfinavir	750 mg tds	Normal dosage
Amprenavir	1 200 mg bd	Normal dosage

* Drug should be administered after the haemodialysis session.
† When saquinavir is used in combination with ritonavir, its dose should be reduced.

GENERAL MEASURES

Nephrologists and physicians taking care of HIV-infected ESRD patients need to be aware of the special issues relevant to HIV-infected patients with ESRD and should co-operate actively with HIV specialists to improve the outcome and quality of life of this group of patients. Prophylaxis against *Pneumocystis jiroveci* pneumonia, tuberculosis and cyto-megalovirus (CMV) in the transplant patient are imperative, while surveillance and early intervention for Kaposi's sarcoma and other malignancies is also important.

CONCLUSIONS

HIV/AIDS is reaching epidemic proportions in southern Africa. With the positive governmental move towards widespread availability of ARV drugs, clinicians are encouraged to gain a sound knowledge of the effects of these agents in patients with and without kidney failure. RRT should be available for

TABLE II. RENAL ABNORMALITIES INDUCED BY ANTIRETROVIRAL DRUGS[13]

Drug	Abnormality
NRTIs	
Zidovudine	Lactic acidosis, rhabdomyolysis
Didanosine	Lactic acidosis, elevated serum uric acid
Zalcitabine	Acute renal failure, lactic acidosis, hyponatraemia, hypocalcaemia, renal calculi
Stavudine	Lactic acidosis, **raised uric acid**
Lamivudine	Lactic acidosis
NNRTIs	
Nevirapine	Lactic acidosis
PIs	
Saquinavir	Lactic acidosis, hypocalcaemia, **hypo/hyperkalaemia**, magnesaemia and phosphoraemia, pancreatorenal syndrome
Ritonavir	Acute renal failure, pancreatorenal syndrome, hypocalcaemia, **hypo/hyperkalaemia**
Indinavir	Lactic acidosis, intratubular precipitation, urinary lithiasis, renal insufficiency
Nelfinavir	Lactic acidosis, hypocalcaemia, lithiasis

those HIV-positive patients who require dialysis, as HAART, their young age and otherwise good health afford them an excellent long-term prognosis.

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CASE STUDY

HIV CARE INTERVENTION – LIMITED RESOURCES, LIMITLESS OPPORTUNITIES

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This case is intended to inspire HIV caregivers and patients that, even in the most trying circumstances of limited resources, AIDS can be managed effectively with highly active antiretroviral therapy (HAART) and perseverance.

Our patient, a 32-year-old man, presented to Themba lethu Clinic with AIDS in November 2004. He had been diagnosed with HIV infection in 2000. At that time he was asymptomatic and attended the state HIV clinic.

His first admission was for *Pneumocystis jiroveci* pneumonia (PCP). At the time our unit was screening patients for a clinical trial. This patient was not our 'usual' trial candidate. He had been expelled from school, had drug and alcohol addictions and a criminal conviction, and was unable to maintain employment (all indicating antisocial personality traits). He also had a history of poor compliance to prescribed medications. Any of these behaviours could have convinced us that he would be unsuitable for the stringent requirements for compliance and clinic follow-up required by clinical trials.

In addition his economic vulnerability could have made study participation complicated. He lives in a shelter for homeless people living with AIDS. This is a scarce resource in South Africa, a country where many people survive on an income of R150/month. This financial reimbursement is the SA Medicines Control Council (MCC) requirement for study clinic visits.

Despite these challenges, the clinic staff were convinced that the patient understood the severity of his disease and that ongoing support would ensure success.

His past medical history included two episodes of pulmonary tuberculosis (TB), in 2003 and 2004 . He was poorly compliant to standard anti-TB drugs (isoniazid (INH), rifampicin (RIF), pyrazinamide (PZA) and ethambutol) during both treatment periods. He also had psoriasis since adolescence.

On initial examination the patient had clinical AIDS, PCP, severe generalised psoriasis, and extensive mucocutaneous Kaposi's sarcoma (KS) lesions. The twice-daily HAART study regimen (lopinavir/ ritonavir 400/100 mg + stavudine 30 mg + 3TC 150 mg bd) was commenced on 19 November 2004. These drugs are available from the South African national antiretroviral (ARV) programme. The pneumonia responded to co-trimoxazole but the pyrexia and anaemia persisted, necessitating readmission in December 2004. Sputum microscopy was now positive for mycobacteria and the retreatment regimen of RIF, INH, ethambutol, PZA, + streptomycin was commenced. At this time the CD4 count was 18 cells/µl and the viral load > 100 000 copies/ml. The lopinavir/ritonavir was replaced by efavirenz because of the potential interaction with RIF. Ultrasound examination showed marked hepatosplenomegaly and numerous small abdominal lymph nodes which were presumed to be consistent with TB or possibly visceral KS.

The patient was admitted for a second time in December because of deterioration in his general condition and also to assist with compliance with these complicated drug regimens.

In January 2005 he developed abdominal pain, vomiting and respiratory distress. Immune reconstitution inflammatory syndrome (IRIS) or a complication of abdominal TB was considered. Intestinal obstruction was excluded and severe oesophageal candidiasis was diagnosed on gastroscopy. The abdominal ultrasound findings remained unchanged.

A Bactec blood culture was positive for *Mycobacterium tuberculosis* complex and *M. avium* complex despite 2 months of TB directly observed therapy (DOT). Bone marrow trephine biopsy on 28 February revealed features consistent with anaemia of chronic disease and a Ziehl-Neelsen stain was positive for mycobacteria.

Fluconazole and azithromycin were added to the regimen. Standard anti-TB drugs were continued while awaiting the Middlebrook indirect susceptibility results.

In March the antibiogram showed resistance to RIF and partial INH sensitivity, susceptibility to ethambutol being retained. RIF and streptomycin were replaced by ciprofloxacin and amikacin and the patient was transferred to a TB hospital. He did not co-operate with staff at this hospital and was returned to our care. A liver aspirate confirmed the presence of granulomatous hepatitis but stains and immunohistochemistry (CD34) were negative for mycobacteria and KS respectively.

The patient developed bilateral oedema and inflammation of the lower limbs in hospital, and a deep-vein thrombosis (DVT) was excluded by Doppler ultrasound.

He was admitted again in May 2005 with worsening abdominal pain, vomiting, new cough and fever and painful feet.

The patient was diagnosed as having KS involvement of the feet, but peripheral neuropathy induced by stavudine or INH could not be excluded. Stavudine was replaced with tenofovir (obtainable by application to the MCC under section 22 on a named patient basis).

A computed tomography (CT) scan showed KS-associated hepatosplenomegaly with focal lesions, pulmonary nodules and a mass in the left ventricle. However, an encouraging sign was that for the first time since commencing HAART 7 months previously he achieved a viral load of < 50 copies/ml and a CD4 count of 179 cells/µl.

In June 2005 he was referred to the oncologists for worsening KS, probably related to IRIS. A skin biopsy confirmed plaque-phase KS, but interestingly stains for HHV8 were negative.

In July the patient arrived at the outpatient clinic with a new episode of fever, insomnia and tiredness. The pharmacy had not been dispensing amikacin, azithromycin and ciprofloxacin. On their reintroduction the symptoms abated. On 27 July he received the first dose of chemotherapy (adriamycin, etopicide) for KS. Surprisingly he tolerated the drugs well and experienced only tiredness, hair loss and anaemia.

We believe that our team's constant vigilance and persistence for 10 months have extended this patient's life. Integral to his care has been regular telephonic and clinic follow-up. Our greatest challenge was ensuring that he obtained the prescribed drugs. To our surprise he was compliant on the 13 different oral medications and 1 intramuscular injection daily for 8 months. One can only imagine the discipline and commitment required. Drug adverse effects and interactions would have overwhelmed anyone with a weaker resolve. He has had 7 admissions and required frequent social, laboratory and radiological monitoring (3 tissue biopsies, 1 CT scan, 3 ultrasound scans, 6 chest X-rays).

Every small improvement in the patient's health gives him a sense of achievement. He has been reunited with his family and has dealt with his feelings of guilt for the suffering he caused them. He acknowledges a second chance at life, recognises his own self-worth and looks forward to a better quality of life. He is now concerned about his future. He faces a number of challenges, as his current shelter is intended for terminal AIDS patients. As he recovers he will have to seek employment in an environment where jobs for unskilled people are scarce. He may no longer qualify for the state disability grant and will have to obtain independent accommodation. Re-entering a social environment in which crime and drug abuse are constant temptations will also be challenging.

The health care team continues to benefit from this experience. Everyday we are faced with AIDS victims who do not have access to ARVs or present too late. The South African ARV programme is in a fledgeling phase where misinformation and stigma regarding AIDS and ARVs still abound. Staff are despondent over overwhelming patient numbers, poor clinical facilities and support.

This case provides proof, and extends our hope, that even in late-stage AIDS and with numerous medical and social problems, and even within a resource-limited public health system, patients can still benefit from our interventions.

Permission: Although there are no clear identifying features, the patient was consulted regarding this publication and permission was granted.

The recent highly successful launch of the KOSH Branch (Klerksdorp/Orkney/Stilfontein and Haartebeesfontein)

From left to right: Dr Binu Luke, Clinical Manager, Tshepong Hospital, Dr Francois Venter, Clinical Director, Esselen Street Clinic and Reproductive Health and HIV Research Unit and lecturer in the Department of Medicine, University of the Witwatersrand (first presenter), Dr Ebrahim Variava, specialist physician and head of the Department of Internal Medicine, Tshepong Hospital, and Tanya Nielson, Research Pharmacist, Aurum Institute for Health Research. (Gavin Churchyard, Chief Executive Officer, Aurum Institute for Health Research, who did the second presentation, and Annette McFarlane, National Key Account Manager Inland HIV Sales Manager – Private Market (Aspen Pharmacare), responsible for arranging sponsorship, are unfortunately not present in the picture.)

DIPLOMA OF HIV MEDICINE (SA): EXAMINATION QUESTION AND MODEL ANSWER

Question: Discuss the relevant issues in preparing a patient for the initiation of antiretroviral therapy (ART).

Model answer:

- Goals of ART, team approach.
- Confirm patient's understanding of HIV status, HIV diagnosis, then stage with CD4+ - viral load, clinical exam.
- Personalise approach, empower patient, understand implications of resistance and how rapidly it occurs and that this Rx is lifelong and not a cure.
- Children and ART: discuss the special challenges especially caregiver understanding and support, refrigeration.
- 'Never an emergency' v. where accelerated approaches (e.g. TB with low CD4 count, pregnancy, advanced disease) may be warranted.
- Support structures for adherence; disclosure as a means of support; religion.
- OI institution, especially co-trimoxazole, trial of OI Rx as adherence test, INH prophylaxis, primary and secondary prophylaxis.
- Depression/mental health/substance abuse/stigma, and access to support groups.
- Contraception, understandings of teratogenicity, clarify desire for family (and what to do if desired!), children and partner HIV status, issues around discordance/concordance and safe sex.
- Employment and lifestyle, any implications for side-effects and ARV selection.
- STI screen, safe sex.
- Predict IRIS, side-effects.
- Smoking, alcohol, exercise, etc.; nutrition and weight gain.
- Grant access, socioeconomic barriers to adherence and support.
- Traditional healers, homeopathy, drug interactions.

CPD QUESTIONS

Journal 22

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

NAME ..... QUALIFICATION .....

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PLEASE INDICATE WHICH OF THE FOLLOWING STATEMENTS ARE TRUE:

1. **Regarding lactic acidosis:**
   Reduced DNA synthesis results in less synthesis of essential mitochondrial proteins. The consequence is the formation of mitochondria which are structurally and functionally impaired, resulting in:
   (a) decreased oxidative capacity of each mitochondrium. Lactate overproduction and cellular dysfunction result.
   (b) increased oxidative capacity of each mitochondrium. Lactate overproduction and cellular dysfunction result.
   (c) decreased oxidative capacity of each mitochondrium. Lactate underproduction and cellular dysfunction result.

2. **Regarding lactic acidosis:**
   (a) Lactic acidosis is diagnosed when pH < 7.35 and/or standard bicarbonate < 20 together with raised lactate. Lactate in this setting is typically > 5.
   (b) Lactic acidosis is diagnosed when pH < 7.35 and/or standard bicarbonate < 30 together with raised lactate. Lactate in this setting is typically > 5.
   (c) Lactic acidosis is diagnosed when pH < 7.35 and/or standard bicarbonate < 10 together with raised lactate. Lactate in this setting is typically > 5.

3. **Regarding drug resistance:**
   (a) Is drug resistance likely to be a *mass* problem in Africa? Mathematical modelling suggests that it will become a widespread problem within the next 5 years.
   (b) Is drug resistance likely to be a *mass* problem in Africa? Absolutely, but mathematical modelling suggests not for at least another 2 or 3 years.
   (c) Is drug resistance likely to be a *mass* problem in Africa? Probably, but mathematical modelling suggests not for at least a decade, and that the impact may be limited.

4. **Regarding drug resistance:**
   It is every clinician's responsibility to reduce the community prevalence of resistance, by looking after their patients responsibly and carefully, by checking adherence at every visit, avoiding drugs that interfere with ARV metabolism, and checking the viral load regularly. This is the same model as for TB treatment – MDR-TB is a product of poor adherence and poor patient follow-up by the health services.
   (a) Fortunately, HIV evolves resistance much slower than TB.
   (b) HIV evolves resistance much faster than TB, so poor management is likely to have rapid consequences.
   (c) HIV evolves resistance at exactly the same rate as TB, so poor management is likely to have rapid consequences.

5. **Regarding skin reactions:**
   Skin reactions, very common in HIV-infected patients, usually occur due to the following agents:
   - trimethoprim-sulfamethoxazole
   - other sulfonamide drugs and
   - various penicillins.

   (a) These drugs account for 45% of all adverse drug reactions.
   (b) These drugs account for 95% of all adverse drug reactions.
   (c) These drugs account for 75% of all adverse drug reactions.

6. **Regarding renal disease and HIV:**
   (a) Renal replacement therapy should be available for those HIV-positive patients who require dialysis, as HAART, their young age and otherwise good health afford them an excellent long-term prognosis.
   (b) Renal replacement therapy should not be made available for HIV-positive patients who require dialysis as HAART, their age and poor health would suggest a poor long-term prognosis.
   (c) Renal replacement therapy should be available for those HIV-positive patients who require dialysis, if they are young, on HAART, do not have resistant HIV and are otherwise in good health.