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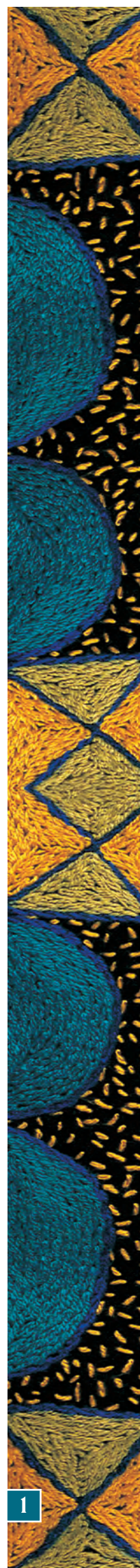
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*Artworks in this edition come from the National Paper Prayers Campaign, initiated and co-ordinated by Artist Proof Studio. This is an initiative which gives South Africans a chance to respond positively and creatively to the AIDS epidemic. The idea of Paper Prayers comes from the Japanese custom of hanging up strips of paper as prayers for healing. Exhibitions have been held nationally and internationally and prayers are sold to raise funds for AIDS organisations. Workshops for health workers, teachers and people living with AIDS can be arranged by ringing Artist Proof Studio (011) 492 1278.*



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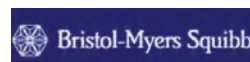
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# FROM THE EDITOR

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We are constantly told that directly observed therapy (DOTS) for tuberculosis treatment has not been a huge success in the developing world. But, once again, we believe that not enough attention is given to counselling around the tuberculosis treatment issue. It simply is not good just to give patients the drugs and leave them to their own devices. So the new catchword is not combination treatment so much as combination counselling. That combination is: time, effort, and culturally appropriate counselling.

**DES MARTIN**

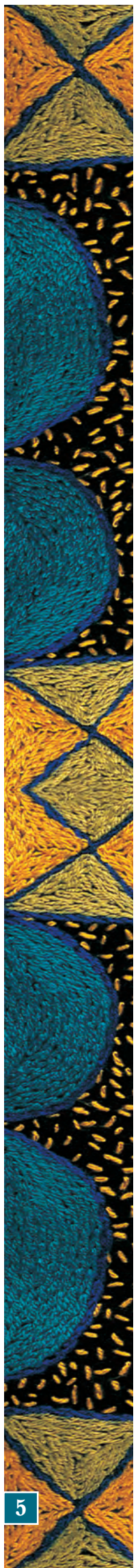
*Editor, Southern African Journal of HIV Medicine  
President, Southern African HIV Clinicians Society*

## COMBINATION COUNSELLING

One wonders how much influence the Iraqi war and planned re-building of that country will have on deflecting and redirecting international focus and funding away from the war against HIV/AIDS in sub-Saharan Africa. We have already seen the impact the war has had on the travel plans of scientists from the developed world (the United Kingdom and the United States of America). As Gerald Friedland said at the recent Boston Retrovirus Conference, 'perhaps more progress would be made if HIV were declared a weapon of mass destruction!'

Highlights of the Boston Conference included impressive presentations on antiretroviral therapy in resource-poor settings, covered in more detail in an article in this issue. At last, feasible, punitive obstacles such as adherence issues were shown not to be the bogeymen that we have all been led to believe. Patients in southern Africa are as adherent as anywhere else in the world.

Good but careful attention to counselling to obtain commitment to lifelong treatment is required and ongoing counselling regarding other associated issues is essential. In other words, the message here is for doctors not simply to write scripts but to counsel patients on side-effects and toxicities (short- and long-term), because once patients understand these issues they are more than willing to commit to lifelong therapy.



## A CRACK IN THE DAM WALL

I feel optimistic! I think that there is at last light at the end of the tunnel, and ART access for all the HIV-infected people of South Africa may just be coming into view. We have a lot to do! To date, despite the World Health Organisation call for expanded access, the South African public sector has had very limited access to antiretroviral agents. For ART to have an impact on the South African epidemic, where it is estimated that 5 million people may already be infected, it will be necessary to establish care structures in the communities that carry most of the disease burden. Implementation of a national HIV treatment programme is likely to require a variety of reproducible delivery models to service areas with different levels of care and infrastructure. There is an urgent need to investigate the various models of ART delivery available in public sector settings in South Africa in order to estimate our national human resource, training and infrastructure requirements more accurately.

This operational research is an amazing opportunity to inform not just ourselves but our continent and the rest of the world. There is real recognition that while there are lessons to be learnt from the developed world our situation in the developing world is different, and we need to find out what is applicable in Africa, culturally and logistically – time is running out.

In order to carry out this type of research it is often necessary to provide ART to a group of research volunteers or people recruited onto programmes for a defined period of time. However, researchers find that drug supply for such research poses a catch-22 situation. A recent editorial in *Science* describes the difficulty that has become central to the ongoing funding of operational research, about which a debate has been raging in the USA. Funders have previously not provided the drugs or the finance to purchase ART. The US National Institute of Health has recently encouraged research on the best ways to



deliver ART to developing countries, but it is concerned that the cost of drugs for such studies would swamp its research budget. A draft policy from NIAID, the AIDS division of the Institute, states that the cost of purchasing drugs would severely restrict the Institute's research capacity by limiting the number, scope, duration and focus of its international HIV-related research activities. The Institute is also concerned that it would be unethical to stop treatment when the trial ends. The editorial in *Science* quotes Professor Bruce Walker from Massachusetts General Hospital in Boston as saying that a limited period on drugs is better than none, that the NIAIDS policy is less than visionary, and that it is stifling research since it is obviously a tall order to expect the researchers to come up with the drugs themselves. The policy has resulted in long waiting periods before these projects can be undertaken, while pharmaceuticals and NGOs are wooed into supplying drugs.

South Africa has a number of internationally approved grants, where building infrastructure and implementation costs are paid for but funding for ART remains outstanding. Most of these projects involve innovative research that will teach us much about ART delivery models and operational issues around drug delivery. Researchers are now trying a variety of well-worn avenues to obtain drugs so that their research can go forward. It was refreshing and encouraging to hear recently that at least one major funder, Secure The Future from Bristol Myers Squibb, is calling for operational research proposals investigating ART provision and that they will provide treatment. Let us hope that others will overcome the difficulties and follow suit. Obtaining these drugs and initiating these projects will be instrumental in breaking down some more of the obstacles to a national ART roll-out in South Africa.

**LINDA-GAIL BEKKER**  
*Managing Editor*

## CONFERENCE REPORT

# CONSIDERATIONS FROM THE BOSTON CONFERENCE

**Des Martin, MB ChB, MMed, FCPATH, DTM&H, DPH**  
*University of the Witwatersrand and SA HIV Clinicians Society*

It is always invigorating and motivational to attend an international HIV conference on another continent and hear about the latest advances and data from other countries. Boston was no exception, and was alive with news on new antiretroviral (ARV) agents and drug targets, structured treatment interruptions, antiretroviral combinations, complications, resistance, comparisons, interactions, therapeutic vaccines, screening protocols, coinfection with GB virus-C, microchip HIV assays and antiretroviral therapy in resource-poor settings.

Not least, Boston, the oldest major settlement in New England, is an impressive city and the Hynes Conference Centre is a very accessible and very comfortable venue for a conference of this stature. Boston and the whole New England region was in the grip of icy blizzards and the city and its parks were covered in a blanket of snow.



At the opening session Dr John Coffin delivered the 8th Annual Bernard Fields Memorial Lecture. He offered some wonderful insights into how the HIV retrovirus has encroached on the human genome. His description of pro-viral remnants of retroviruses (human evolutionary retroviruses – HERVs) as molecular fossils demonstrated the frailty of humanity against the onslaught of repeated integration of novel DNAs. Eight per cent of the human genome currently consists of HERVs. Dr Coffin posed the

intriguing question as to whether these fossil retroviruses could ever come back and cause human disease.

The 42nd president of the United States of America, William Jefferson Clinton, delivered a keynote lecture. President Clinton is a superb orator and held the attention of the packed auditorium. He has established the Clinton Foundation, which is involved in various aspects of delivery of AIDS care. President Clinton paid tribute to ex-President Mandela for his commitment to and action in the fight against HIV/AIDS. He also spurred the attendees to worldwide action not only against the virus but also against barriers to care and cure. The main body of his talk related to the development of infrastructure that would be necessary before any form of ARV therapies could be introduced to populations. He cited examples where existing infrastructure facilitated the delivery of ARVs in various parts of the world, including Uganda, Asia and Haiti.

### HORIZONS IN ANTIRETROVIRAL THERAPY (ART)

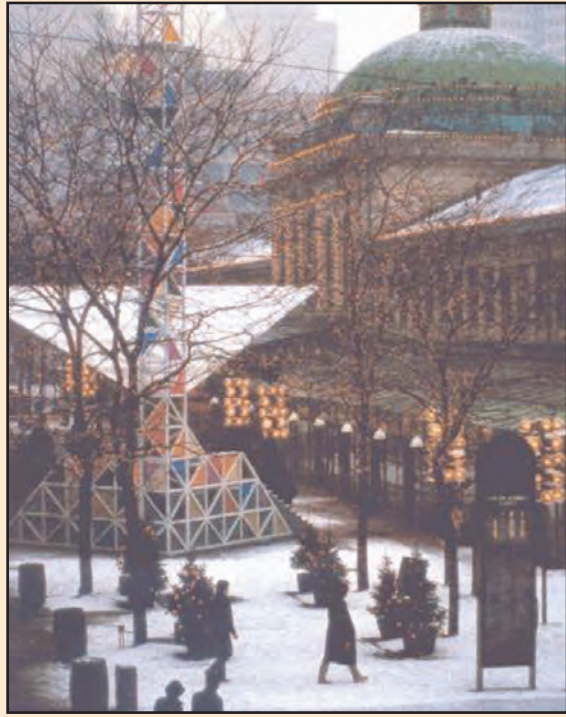
A common theme throughout many presentations focused on the challenges presented by existing drugs:

- evolution of drug resistance in some patients, and
- persistence of HIV in the body in all patients.

In an attempt to address these challenges the goals of new drugs were to:

- improve the acceptability and tolerability of current drugs
- find new agents that might have improved activity throughout the body, and
- find agents that will be active against viruses that have already evolved.

Sessions on new drugs reflected the benefits of two decades of experience with HIV, advances in virology, protein structure modelling and drug candidate screening. It has sometimes been possible to overcome many of the problems of older formulations by using sophisticated engineering methodologies. It is encouraging to know that there are a number of products



in progress for use, not just one or two.

It is hoped that drug innovations in existing classes and the emergence of new classes of ARVs indicate that, in the best of worlds where ARVs are available to all HIV-infected persons, drug-resistant HIV may not be a major problem in the years to come.

#### NEW DRUGS AND TARGETS

Until recently, ARV drugs have been required to be incorporated into the cell in order to do their job, but they can be neutralised by some cells, using self-defence mechanisms such as 'efflux pumps' which sense toxins and eject foreign material from inside cells. Many experts believe that this kind of cellular resistance could be an important reason for viral persistence and evolution in patients on seemingly potent combination therapies.

In the search for new agents, scientists have wondered if equally potent drugs targeting the parts of the virus life cycle that occur outside the cell might be better than drugs targeting events that take place inside infected cells.

Last year saw the first drug in the fusion inhibitor class (T20) reach clinical practice and some exciting proteases reach licensing stage.

In a plenary lecture (session 23), Eric Hunter from Alabama reviewed the progress of entry inhibitors and prospects for further development of extracellular ART. This lecture emphasised the multiple steps involved in the

process of HIV attachment and entry into cells, and explained how each of these steps could be targeted. The first step is HIV's gp120 molecule binding to a CD4+ receptor and to a necessary 'co-receptor' molecule on the cell surface (CXCR4 and CCR5 are the most common) that must be present on the cell surface for proper attachment. Drugs inhibiting this binding are called attachment inhibitors.

During the first morning's oral sessions the progress of the following new ARVs was discussed:

- two new protease inhibitors (PIs)
- a class of non-nucleoside reverse transcriptase inhibitors
- pyranodipyrimidines (HIV integrase inhibitors), a novel group of agents working on 3' processing of integrase
- exciting blockers of the CCR5 co-receptors
- a betulinic acid derivative, and
- a second fusion inhibitor T-1249.

A delectable line-up, but possibly initially too expensive for clinicians from the developing world, in which cost plays such a major role in access.

#### FUSION INHIBITORS

T20 or Fuzeon, the first direct inhibitor of gp41-mediated fusion, was proven sufficiently active to receive FDA approval for use in heavily ARV-experienced patients. Administered twice daily by subcutaneous injection, it is in limited expanded access usage.

In a concise summary of pooled safety and efficacy data from its two phase III studies (Toro 1 and Toro 2, presented by J-F Delfraissy *et al.* – Abstract 568) in which > 600 highly pre-treated patients received optimised therapy with or without enfuvirtide, the drug was reported to have reduced HIV RNA levels by 10 - 100-fold in the enfuvirtide-treated group in both trials. Almost 98% of patients had injection site reactions to enfuvirtide in the studies, but local reactions led to discontinuation of treatment in only 3% of patients. A concern was introducing bacteria into the blood, and while there was a significant increase in the rate of bacterial pneumonia in patients on enfuvirtide in Toro 1 and 2, the trend to more bacterial infections was not significant overall. Another theoretical concern is allergy, and although only 2 cases of proven allergy to the drug was documented in these trials, 10% of patients developed raised eosinophil counts, suggesting a tendency towards allergy.

The high estimated cost of the new drug and the common occurrence of cosmetically bothersome (if not medically very serious) reactions is likely to limit use to very highly motivated patients with few other treatment options.

T-1249, son of T20, is a second-generation Roche fusion inhibitor. It is an injectable peptide very similar in design to enfuvirtide but binding to gp41 just downstream of enfuvirtide's gp41 binding site. There are no orally available fusion inhibitors currently in development.

T-1249 has recently been tested in phase I/II trials for activity against enfuvirtide-resistant viruses. T-1249 was given to 23 patients with both genotypic and phenotypic resistance to T20. They were treated for 10 days and a >10-fold decrease in viral load was noted in 63% of patients. There was one possible allergic reaction. The activity of the drug against enfuvirtide-resistant virus may make its use in sequence possible for patients who have failed previous enfuvirtide treatment.

### ENTRY INHIBITORS

Previously proposed entry inhibitors have only been injectable, some requiring hours-long infusions. PRO542 (Progenics), a novel tetravalent CD4-Ig fusion peptide, and TNX-355-01 (D R Kuritzkes *et al.* – Abstract 13) are the latest candidates for this type of injectable therapy, targeting areas on gp120 to prevent attachment. The pipeline is, luckily, now filling up with 'small-molecule' compounds that bind to and inhibit the co-receptors CXCR4 and CCR5. They are generally absorbed better from the gastrointestinal tract, making oral therapy possible. One such CCR5 inhibitor from UK-427, 857, presented by P Dorr *et al.* (Abstract 12), is in phase I dose-ranging human studies without any untoward side-effects to date.

Two additional CCR5 inhibitors with pill form potential are currently in preclinical development. One is TAK 220, researched by Y Iizawa *et al.* (Abstract 11), and the other is from Ono AK602 (K Maedak *et al.* – Abstract 10). AnorMed's AMD 3100 is no longer in development, but another of their formulations, CXCR4 inhibitor AMD070, is showing promising preclinical results.

Observers are paying close attention to the attachment inhibitor area, partly because it has the theoretical potential to cause serious toxicities. CXCR4 and CCR5 are present on cells from many types of tissues and have a myriad of functions, including normal functions such as growth and development. The effects of interfering with these molecules in normal tissue are unknown. The first CCR5 inhibitor was discontinued as a result of serious cardiac side-effects. Another potential theoretical drawback is the 'co-receptor switch', enabling viruses to use either CXCR4 or CCR5 more efficiently. It has often been noted that many more so-called 'X4' viruses are present in patients with late-stage AIDS, while people with very early infection nearly always have a dominant

'R5' virus population. The possibility that inhibiting virus attachment to CCR5 would somehow cause a switch to CXCR4 use – and more importantly, that this switch might hasten patients on the road to AIDS – is worrying. Most early clinical trials of CCR5 inhibitors have not shown R5X4 switching to take place in the short term.

### HIV INTEGRASE INHIBITORS: PYRANODIPYRIMIDINES (PDPs)

This novel group of agents inhibit an integration step (3 processing of integrase) that is different from both clinically approved ARVs and other integrase inhibitors such as the diketo acids. Integrase is of course the enzyme responsible for inserting the viral cDNA into the host cell chromosome. PDPs can be considered candidate drugs to be further pursued in their own right and in drug combination regimens.

### RNA INTERFERENCE: A NEW TARGET

Mario Stevenson and John Rossi co-chaired a symposium (Abstracts 49 - 52) examining the various aspects of 'RNA interference' or RNAi. RNAi is a recently described self-regulatory process that cells use to shut down production of given proteins when they detect excess accumulation of short, double-stranded RNA coding for those proteins inside the cell. HIV researchers have hypothesised that introducing short interfering RNA bits into cells could stop HIV production, and as summarised in this symposium, there is hope that this may be clinically applicable. Dr Judy Lieberman and others showed surprising evidence that exposure of HIV-infected cells to interfering bits of RNA in the test tube could shut down HIV production by these cells. In other words, the RNAs worked even if they were not produced by the cells themselves. In an animal model using a different disease (autoimmune hepatitis) Dr Lieberman went on to show that interfering RNAs could actually be taken up in large amounts into cells when injected into animals. Together, these preliminary findings may open up an entirely new approach to HIV therapeutics: one can imagine infusing patients with interfering RNAs that would completely shut down HIV replication. The potential for this approach is totally unknown and we eagerly await updates over the coming months.

### PROTEASE INHIBITORS

1. The RO-033-4649 (Roche) developed through their optimised synthesis programme should be highly potent, be easily ingested by mouth, and have manageable and predictable interactions with other drugs. (It appears to interact only moderately with CYP3A4 but with no *in vitro* induction.) Its major feature is its potent and persistent



activity against HIV with high levels of resistance to currently available PIs. (Trials showed no significant loss of activity against a panel of triple site-directed mutant viruses.)

Phase I clinical studies are currently underway. Human studies have yet to be commenced.

2. The TMC114, Tibotec PI, now in the early stages of clinical trials, has been tested in liquid gel form in a group of 50 PI-resistant patients in combination with ritonavir. It was assessed at three dose levels, given for 14 days, before subjects moved on to an optimised salvage regimen. According to phenotype, 46% of subjects were resistant to all drugs with 27% sensitive to one agent, 3% to two, and 24% to more than two. At 2 weeks, 42% of subjects had reached > 400 copies/ml and viral load was still decreasing in all patients with a maximum HIV RNA decline of 2.49 log<sup>10</sup> copies/ml. Diarrhoea (32%), flatulence (18%) and dizziness (11%) appeared to be the major adverse effects.

#### NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS (NNRTIs)

Benzophenone analogues GW4751, GW4511 and GW3011, from GlaxoSmithKline, are potent new NNRTIs active against both wild-type virus and a broad spectrum of NNRTI-associated mutant viruses including those known to be highly resistant to currently available NNRTIs. In a trial reported by J Chan *et al.* (Abstract 6) inhibitory concentration (IC<sub>50</sub>) of human serum protein binding was modest and cytotoxicity was low.

#### MATURATION INHIBITORS: BETULINIC ACID DERIVATIVE

PA-457 (Panacos Pharmaceuticals, Maryland) is a small-molecule inhibitor of HIV-1 budding/maturation that potently inhibits replication of virus isolates resistant to all classes of approved drugs. It has been shown to have no cross-resistance to any other ARV and acts at a late step in the virus life cycle, causing a defect in gag processing (p25 to p24 processing is inhibited). It has an IC<sub>50</sub> of 6.1 mM and in its present form has a bioavailability of 60%, but is being tried in a new salt formulation in ongoing clinical trials in order to optimise bioavailability.

#### 2NN STUDY

One of the most eagerly anticipated clinical trials of the conference was the 2NN study. This was the first large, prospective study to compare two NNRTIs, nevirapine and efavirenz, head-to-head (F von Leth *et al.* – Abstract 176, results presented by Joep Lange). This was a large, multinational (65 centres from 17 countries) industry-

sponsored open-label trial. A total of 1 216 antiretroviral-naïve patients were randomised to receive one of four regimens:

- D4T plus 3TC plus nevirapine 400 mg once daily
- D4T plus 3TC plus nevirapine 200 mg twice daily (standard schedule)
- D4T plus 3TC plus efavirenz 600 mg once daily
- D4T plus 3TC plus nevirapine 400 mg plus efavirenz 800 mg once daily.

Twice as many patients were randomised to the twice-daily nevirapine and once-daily efavirenz arms (standard dose schedules) as to the other two treatment groups. The primary outcome was treatment failure at 48 weeks, which was a composite end-point of virological failure (two consecutive viral loads > 50 copies/ml or < 1 log decline at 12 weeks), HIV disease progression, or drug intolerance.

At baseline, the participants were demographically diverse and had relatively advanced HIV disease, and 21% had a prior AIDS-defining condition.

At the end of the study, treatment success was observed in 56.4%, 56.3% and 62.3% of the nevirapine once daily, nevirapine twice daily and efavirenz arms, a statistically insignificant difference. There was a higher drop-out rate due to adverse events in the nevirapine plus efavirenz arm, so only 46.9% of patients in this group attained treatment success. This was significantly lower than in the efavirenz-only arm. At the highest viral load strata, there was a trend toward efavirenz being more effective than either dose of nevirapine, but again this did not reach statistical significance. More hepatotoxicity was observed in the nevirapine-containing arms (in particular, once-daily dosing), while more central nervous system side-effects were observed in the efavirenz-containing arms, but the overall rate of treatment discontinuation for toxicity was similar across all 3 single-NNRTI arms. Importantly, there were 2 nevirapine-related deaths, one due to Stevens-Johnson syndrome complicated by methicillin-resistant *Staphylococcus aureus* (MRSA) bacteraemia, and the other due to hepatitis; no treatment-related deaths were associated with efavirenz use. Changes in lipid parameters were more favourable in the 2 nevirapine arms compared with the efavirenz arm, with significantly better improvement in high-density lipoprotein (HDL) cholesterol levels and in the total cholesterol/HDL ratio.

#### STRUCTURED TREATMENT INTERRUPTION (STI)

STIs have always seemed an attractive therapeutic option. Benefits include reduction of time on drug, reduced toxicities and reduced costs. The potential risks have been





related to issues of adherence, symptoms related to viral rebound, CD4 cell loss and viral resistance. New research and new strategies have emerged which deserve further investigation. However the subject of STIs still remains controversial.

The whole issue of STI has been subjected to several prospective randomised trials. Various aspects and strategies of STIs have now been studied:

#### ISSUES OF SAFETY

A study presented by J Ananworanich *et al.* (Abstract 64) investigated the randomisation of 74 patients (CD4+ counts > 350 cells/ $\mu$ l and viral load < 50 copies/ml). There were three arms to the study. In the first arm patients continued their treatment, in the second arm patients were on a fixed week on/week off regimen, and in the third arm patients were given stop and start medication when their CD4+ cell count fell below 350. At 48 weeks the results showed that the CD4-guided arm (arm 3) and the week on/week off arm (arm 2) had comparable clinical adverse events and quality of life (QOL) outcomes to continuous ARV (arm 1). The highest treatment failure rate was in arm 2, and the most cost-effective arm was arm 3 with only 33% of time spent on ARVs.

A group of Spanish investigators (I Ruiz *et al.* – Abstract 65) randomised 120 patients to a 48-week trial comparing continuous treatment with treatment stopped and started on the basis of predetermined cell count and viral load criteria. These criteria were a viral load > 100 000 copies/ml and CD4+ count < 350/ $\mu$ l and any opportunistic infection. Patients enrolled in the study had an undetectable viral load for a year and a CD4+ count > 500 for at least 6 months. Of interest, 44% of patients were able to remain off treatment for the duration of the study. A high pretreatment CD4+ count predicted success after stopping medication. Forty per cent of patients in the STI group had some clinical complications, including 1 patient who had a fully blown acute retroviral syndrome.

#### RESISTANCE

Stefano Vella (Abstract 66) presented interim safety analysis of 273 patients who were randomised to continue treatment or to cycle on and off medications at progressively longer intervals (1-month to 3-month cycles). The genotypic results obtained were presented after three STI cycles, by which stage the percentage of patients in the STI group with at least one resistance mutation had increased slightly from 13% to 19%. Most mutations were against nucleoside reverse transcriptase inhibitors (NRTIs) and 60% had been present in baseline samples. The virological response to treatment was 100%

in patients without mutations and 92% in those with at least one mutation, suggesting that these results may ultimately affect treatment success.

The late-breaking results from a National Institute of Health study which randomised 56 patients to continuous treatment or a 4 weeks off/8 weeks on schedule showed an alarming incidence of resistance mutations. The genotype results showed emergence of new mutations in 3 of 8 individuals on interrupted efavirenz-based regimens. The study was closed to further enrollment because of these results, and investigators urged caution in using NNRTIs and 3TC in STI settings.

#### SALVAGE THERAPY

A CPCRA trial (J Laurence *et al.* – Abstract 67) randomised 270 late-stage patients with therapeutic failure (mean CD4+ count 180 cells/ $\mu$ l, 50% at clinical diagnoses of AIDS) to a 4-month STI before starting salvage. This group was compared to the group who continued therapy. Clinical complications of AIDS occurred in 22 STI patients and 12 controls. There were 8 deaths in each group. The excess events in the STI group prompted the study data safety and monitoring board to close it prematurely.

Markedly different results came from a French study (C Katlama *et al.* – Abstract 68) which randomised 68 late-stage patients with treatment failure to immediate salvage therapy with 8 or 9 antiretroviral drugs (GIG HAART) or to an 8-week STI prior to salvage. The mean CD4+ count of enrolled patients was < 50 cells/ $\mu$ l and 68% had clinical diagnoses of AIDS. At week 24 of salvage, the viral load had dropped 1.09 log in the STI group versus 0.29 log in the continuous group and the CD4+ count had risen by 69 cells in the STI group versus 7 cells in the continuous group. Clinical events occurred at similar rates in both groups.

#### THERAPEUTIC IMMUNISATION AND STI

E Harrer *et al.* (Abstract 60) presented a study of the safety and immunogenicity of a modified vaccinia Ankara (MVA) vector expressing HIV-1 Nef in 14 patients with plasma HIV RNA < 50 copies/ml and CD4 > 400 cells/ $\mu$ l. Patients were given 3 doses of the immunogen at weeks 0, 4 and 16; 2 weeks after the final immunisation, they interrupted their ARV therapy. Other than local inflammation and systemic effects, the immunisations were well tolerated. Following 3 immunisations, 7/14 patients recognised new cytotoxic T lymphocyte (CTL) epitopes and 3/14 had Nef-specific CD4T cells. The mean pre-ARV treatment plasma HIV RNA level was approximately 20 000 copies/ml; following immunisation and STI the mean viral load was 46 000 copies/ml.

In a trial of ALVAC, R Tubiana *et al.* (Abstract 61) administered 4 immunisations over 12 weeks in 48 patients receiving ARV therapy with a viral load < 200 copies/ml and CD4 > 400/ $\mu$ l; at week 16 ARV therapy was interrupted. No significant clinical events were recorded. Thirty-six patients with low CD4 proliferation stimulation index (mean 3.3) to p24 antigen before immunisation had a mean SI of 6.8 at the time of interruption. There was a 3-fold increase in CD8 responses after resuming therapy.

In an interesting twist, Y Levy *et al.* (Abstract 62) presented data from 70 patients who received ART alone (37 patients) or 4 ALVAC immunisations every 4 weeks followed by 3 cycles of subcutaneous interleukin (IL)-2 every 8 weeks. At 40 weeks after the final IL-2 dose, all patients stopped ARVs. Sustained CD4 proliferation to p24 antigen at week 36 was noted in 15/32 immunised patients versus 8/33 controls, time to virological failure was statistically different between the groups but only by 13 days (42 v. 29), and 2/37 (5%) controls versus 8/33 (24%) immunised patients remained off ARVs at week 52.

Although therapeutic immunisation remains the greatest hope for the future, and it was encouraging that the immunogens used were safe and well tolerated, the virological results were less than impressive. In fact, there did not seem to be a difference between the group that had undergone therapeutic immunisation and the group that had undergone several cycles of STI alone.

#### ARVs IN RESOURCE-POOR SETTINGS

Session 33 (Abstracts 168 -175) was devoted to the studies and projects on ARV therapies from South Africa, Tahiti, Malawi, Uganda, Senegal, India and Mozambique. Individually and taken together, these studies have revealed that ARV therapies can be successfully introduced into resource-poor settings. Furthermore, treatment success can be achieved with fewer technological resources and adherence to medication can be excellent. The problems revealed in these studies have been related to drug access, reliable medicine supply and the costs of treatment. Only the presentation from Senegal (A 173) and Mozambique (A 175) reported on government-initiated and supported programmes. Of note was the successful use of inexpensive ART in India (A 174), Malawi (A 172) and Mozambique (A 175).

Paul Farmer delivered an animated presentation related to his experiences in a rural clinic in Haiti. He reported that the 'transnational outcome gap' was growing at an alarming rate, noting the discrepancies between resource-poor and resource-rich settings. He used clinical parameters alone as indicators for initiation of therapy,

monitoring and outcome. In this setting CD4+ cell counts and viral load measurements were not available. His clinical parameters related to weight gain, QOL, and reductions in hospitalisations, new opportunistic infections and mortality. His experience shows that CD4+ cell counts and viral load testing, although very useful, are not a prerequisite for instituting treatment programmes.

Once again these presentations demonstrated that although treatment is becoming more widely available, in resource-poor settings only a tiny fraction of those who could benefit have been able to access it. As Gerald Friedland stated, 'perhaps more progress would be made if HIV were declared a weapon of mass destruction.'

Dr Jean Nachega (Abstract 169) showed that in a population of HIV-infected adults in Soweto, South Africa, the baseline knowledge of the causation of HIV, mode of transmission, perceived benefits of ART and the importance of ART adherence was high.

#### DIAGNOSTICS

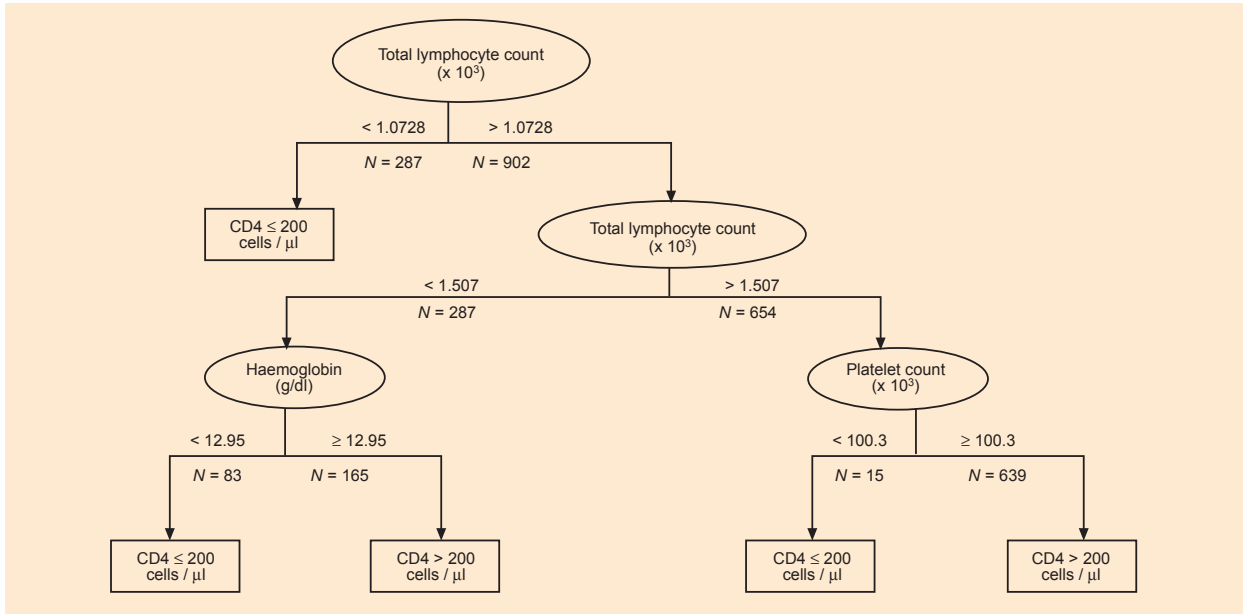
Resources and laboratory capacity in developing countries remain limited. Inexpensive methodologies and strategies are therefore of interest to people working in these settings. An interesting study evaluated the use of the total lymphocyte count in 1 189 patients (R Y Chen *et al.* – Abstract 168). The researchers found that by using data derived from the full blood count they were able to develop a decision tree analysis to predict a CD4+ count of < 200 cells/ $\mu$ l. Their model had a sensitivity of 91%, specificity of 73% and positive predictive value of 88%.

Two presentations evaluated the use of p24 antigen assays as a surrogate for viral load. In one presentation, an HIV-1 quantitation kit based on a modification of the p24 antigen assay was evaluated in both B and non-B subtypes to determine whether it could be used as a substitute for viral load (R Respass *et al.* – Abstract 669). The results showed that there was a significant correlation between viral load and the p24 antigen assay, independent of subtypes tested, and it would therefore provide a less expensive approach to viral testing in resource-limited settings. In contrast, however, a group evaluated serum samples from Rakai, Uganda (L A Spacek *et al.* – Abstract 670), utilising a heat-denatured p24 antigen assay. Their results showed a weak correlation with standard HIV-1 RNA viral load assays.

#### PATHOLOGY OF AIDS

In a plenary lecture, Sebastian Lucas from London delivered a fascinating global perspective on clinical pathology of AIDS. Two decades' study of the tissue





The FBC decision tree.

pathology of HIV/AIDS has revealed marked geographical differences. New entities and pathological variants are still being described. Socioeconomic differences and access to medical care impact on clinical presentations in resource-poor countries. There is more tuberculosis, less non-TB mycobacteriosis, less *Pneumocystis carinii* pneumonia (PCP), less lymphoma and less HIV encephalitis compared with industrialised countries, while geographically restricted conditions have significant local impact (e.g. leishmaniasis, histoplasmosis and penicilliosis). Clearly IV drug use determines the amount of hepatitis C virus (HCV) coinfection and subsequent liver disease. Some conditions have a similar disease profile locally (e.g. cryptococcosis and candidiasis). Interestingly it has been shown that HIV-infected immigrants take on many of the clinical pathology patterns of the host country once they are absorbed into local medical systems. Diet determines the frequency of toxoplasmosis (highest in Francophone countries) and probably affects gut protozoal infections. ARV therapy has profoundly altered the pathology of HIV disease with a decrease in incidence of lymphoma, Kaposi's sarcoma, PCP and TB. Of interest has been the paradoxical enhancement of certain conditions when commencing ARVs, particularly TB, other mycobacteriosis, cryptococcosis and herpesviruses through immune reconstitution. New patterns of drug toxicity are now encountered (hepatic steatosis and lactic acidosis). The pathology of HIV in the next decades will be determined by the longer-term survival of individuals and will manifest in the form of chronic degenerative diseases, e.g. atherosclerosis and coronary artery disease.

### TUBERCULOSIS (TB)

TB has emerged as the leading worldwide cause of morbidity and mortality in HIV. In a symposium Professor

Richard Chaisson of Johns Hopkins, Baltimore, discussed the need for new approaches when dealing with TB in areas of high HIV prevalence. The currently practised traditional control measures such as passive case-finding, treatment of latent infection, BCG vaccination and treatment of TB-infected individuals have not controlled the burgeoning HIV-associated TB epidemic. This has been demonstrated both in resource-rich and resource-poor settings. He emphasised that improving TB control will require an expansion of directly observed therapy (DOTS) programmes, active case-finding, using every contact opportunity for evaluation of active disease, aggressive treatment of latent infection, and widespread use of ARV drugs.

It has been shown that in South Africa (Badri *et al.*) significant TB reductions (80%) were seen in individuals at all levels of CD4+ count when highly active antiretroviral therapy (HAART) was used, most notably among those with CD4+ cell counts below 200/µl and also in the stratum 200 - 350/µl. These findings would suggest that commencing ARVs at the CD4+ threshold of 200/µl will therefore miss a significant number of cases.

Professor Chaisson made a strong statement about integration of HIV and TB services, and a pilot study being carried out in Durban, South Africa, was reported by G Friedland *et al.* (Abstract 783). In this study, patients at TB clinics are screened for HIV and if positive are offered ART. A once-daily regimen of ddI/3TC and efavirenz together with standard TB DOTS is given. Twenty patients have been enrolled and at the 4-month time point the viral load is below 50 copies/ml in 78% and there has been a mean rise of 69 CD4+ cells. The medication has been well tolerated and there have been no serious side-effects. TB sputum clearance has been > 90%. Another case series

using concomitant efavirenz 600 mg daily with TB therapy containing rifampicin was highly successful in treating both diseases, although in this study the substantial rate of side-effects and toxicities cautioned against simultaneous administration (Abstract 784).

Two studies investigated the efficacy of efavirenz at the 600 mg dosage in HIV patients receiving rifampicin-based regimens in the treatment of their TB (A Patel *et al.* – Abstract 138, and D Pedral-Samapio *et al.* – Abstract 784). In both studies the standard dose of efavirenz was effective. Of interest, the incidences of immune reconstitution syndrome were 8% and 11% respectively in the above studies.

### ACUTE PRIMARY INFECTION

Immunologists and virologists have been very interested in studying patients with recent HIV infection. This has provided more information regarding the pathogenesis of HIV disease and potential benefits of early intervention. From a public health perspective the diagnosis of recent infection using the serological testing algorithm for recent HIV seroconversion (STARHS) assay has been recommended for epidemiological studies for seroincidence. Until now no studies have convincingly demonstrated that diagnosing recent infection has implications for control of HIV infection. Data presented from a study of discordant couples in Rakai, Uganda (M J Wawer *et al.* – Abstract 40) suggest that the risk of HIV transmission per coital act is highest following seroconversion (0.0082 per coital act) and during the 2 years before death (0.0045 per coital act). Overall approximately 50% of all HIV transmissions in Rakai occurred within 5 months of index partner seroconversion. Similar data were presented by CD Pilcher *et al.* (Abstract 154) from Malawi, who found that 2.5% of men in a Malawi STD clinic, including 4.5% of those who tested HIV antibody-negative, had acute HIV infection. These two studies have dramatic indications for HIV prevention programmes: patients who test HIV negative may in fact be those most likely to transmit the virus.

The issue of autoimmunisation and immune control of HIV infection has been a focus of study by the group led by Bruce Walker. In these studies to date he has followed a cohort of patients who were treated during acute HIV infection, which was followed by multiple STIs. This was done in an effort to preserve HIV-specific CD4+ responses and thus promote immune control of HIV infection. In a Kaplan-Meier evaluation of time to reach > 30 000 copies/ml of plasma HIV RNA, 40% of patients who underwent STI had < 30 000 copies/ml at 900 days compared with approximately 25% of a control cohort. Although these data may suggest an advantage to STI in an acute HIV infection, loss of control in a certain number of patients treated during acute infection, where STI

potentially has the greatest autoimmunisation impact, may not bode well for similar strategies in chronic HIV infection.

A number of presentations on treatment started during acute infection which was followed by STIs yielded similar results, in that the strategy was beneficial in a limited number of patients. These results are still preliminary and at this time ART in acute infection should probably be limited to the context of a clinical trial.

### GBV-C AND HIV

A group of oral and poster presenters provided a lively and provocative debate on the significance of GBV-C virus in the development of HIV disease. This virus is found in 1.8% of blood donors and 15 - 20% of patients with HCV. GBV-C in itself does not cause clinical hepatitis. The intriguing finding that GBV-C inhibits the replication of HIV *in vitro* (S I George *et al.* – Abstract 847) and its strong association with improved outcomes in HIV stimulated debate. J P Aboulker *et al.* (Abstract 849) showed that patients infected with this virus had greater and more sustained increases in CD4+ cell counts and fewer HIV-related clinical events on ART. A similar finding was shown in the MACS cohort presented by C Williams *et al.* (Abstract 159LB). P Bjorkman (Abstract 157) showed an association between the loss of GBV-C viraemia and progression of HIV disease and suggested that GBV-C viraemia might be a secondary phenomenon that is lost as HIV progresses. Other work seems to suggest that GBV-C directly influences HIV replication.

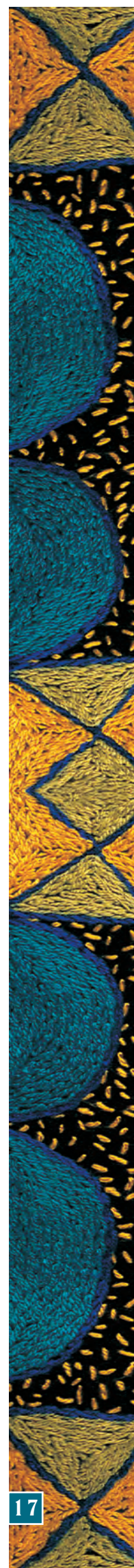
### VACCINES

The ideal vaccine would be one that is safe, induces cross-clade immunity, and effectively prevents infection. Worldwide control of the pandemic is dependent on the effort to succeed.

Dr Mark Feinberg explained the importance of the role of animal models in vaccine evaluation, and an investigator from the HIV Vaccine Network, Dr Scott Hammer, presented an update on vaccine clinical trials. He listed various requirements for successful trials including political commitment, community participation and education, cultural consideration, seroprevalence and seroincidence data, molecular dynamic data, suitable site selection and industry collaboration.

The preventive HIV vaccine field has made important progress in recent years with the results of the first phase III trials expected imminently. There are numerous novel vaccine candidates soon to enter human trials.

Biological targets of vaccines currently include CD8 cytotoxic lymphocytes, CD4 lymphocytes and neutralising antibodies (NAs). Vaccine approaches include protein subunit vaccines that induce antibodies, recombinant





peptide-based vaccines, DNA-based vaccines, and vector-based as well as viral-like particles. A long list of viral vectors include adenovirus, canarypox, and vaccinia Ankara. There are also bacterial and fungal vectors that target mucosal immunity and dendritic cells.

Efforts to produce sterilising immunity by vaccination have been revived. B S Peters *et al.* (Abstract 424) demonstrated that alloimmunisation occurs during intercourse in both the female and (to a lesser extent) the male partner, a phenomenon that the researchers believe represents a physiological function that enhances immunity to sexually transmitted pathogens. F M N Bertely *et al.* (Abstract 453), using an animal model, demonstrated that mucosal immunity, which may be a requirement for protection against HIV, can be induced by a DNA vaccine administered via the nasal mucosal passage.

### KEY THERAPEUTIC DECISIONS IN MANAGING HIV INFECTION

This symposium was the concluding academic discussion of the conference. It was convened by John Mellors (University of Pittsburg School of Medicine, Pa, USA) and Suzanne Crowe (Burnett Institute, Melbourne, Australia).

#### INITIATION OF ART

The first speaker was Marty Hirsch (Harvard Medical School), who discussed when to commence ARVs and what first-line regimen to use. There are certainly major outcome differences between those who start therapy when the CD4+ cell counts are below or above 200/ $\mu$ l. In the stratum 200 - 350/ $\mu$ l the differences in outcome are less clear cut. In addition, some studies suggest that viral load levels may help guide decisions whereas others do not. It is generally accepted that at levels below 200/ $\mu$ l ART treatment should be given and that at > 350/ $\mu$ l treatment could be deferred. Between 200 and 350/ $\mu$ l treatment should be considered, especially if the rate of decline of CD4+ cells is excessive (>100 per year) or the viral load is between 50 and 100 000 copies/ml. These guidelines are likely to change when therapies improve and the drugs become less toxic.

With regard to first-line regimens the potency of combinations depends on how they are combined. Four-drug regimens have no real advantage and have the disadvantage of increasing toxicities (and cost). The combination of AZT, 3TC and efavirenz appears to be the standard to which other regimens can be compared. Other potentially good initial regimens are tenofovir, 3TC and efavirenz or D4T and 3TC with lopinavir.

#### WHEN TO SWITCH ARVs

This talk was given by Steven Deeks (University of California). The definition of virological failure is a viral

load > 50 HIV RNA copies/ml. In the threshold of viral load between 50 and 200 copies/ml the development of resistance is inevitable. The recommended approach for most patients experiencing incomplete viral suppression with their first and second regimens is to modify treatment as soon as possible, thus preventing the development of drug-resistant mutations ('switch early, switch hard'). The question of when to switch therapy for heavily treated patients with limited therapeutic options is not clear. Such patients have three broadly defined options: switch to an aggressive regimen with the goal of maximal viral suppression; interrupt all therapy; or continue a partially effective regimen despite the presence of drug-resistant HIV. Many patients do well for years despite incomplete viral suppression. The CD4+ count often remains stable, the reason being that resistant virus depletes CD4s at a slower rate owing to an impaired replicative capacity. The problem with treatment interruptions relates to rebound wild-type virus with consequent immune activation and loss of CD4 cells.

#### WHAT ARV TO SWITCH TO

This talk was given by Patrick Yeni (Paris, France). One of the problems compromising choice of agents is cross-resistance of drugs within classes, thus limiting the number of active drugs available for rescue therapy. Resistance testing therefore becomes important in helping to make treatment decisions. Therapeutic drug monitoring has proved to be problematic in informing treatment decisions. In general terms, strategies would include drug recycling, treatment intensification, boosted PIs and PI combinations.

#### WHEN TO INTERRUPT ART

In broad terms treatment interruptions have been studied in both acute and chronic HIV infection (H Guenthard, Zürich, Switzerland). These trials have mainly addressed three questions:

- whether protective immune responses may be induced
- whether drug exposure can be limited in order to minimise toxicity and reduce costs, and
- whether response to salvage regimens in patients with multiple treatment failures can be improved.

These potential benefits have to be weighed against the potential risks of the strategy, such as CD4 cell decline, selection of viral drug resistance, increasing risk of HIV transmission, emergence of acute retroviral syndrome, reseeding of viral reservoirs, and potential decrease of adherence to subsequent therapy.

At present there are still many unanswered questions, and this strategy cannot yet be recommended in routine clinical practice.

## CASE STUDY

# HIV TESTING IN ADOLESCENTS — AN ETHICAL DILEMMA

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A 14-year-old girl is brought to a general practitioner by her mother. They say that she has been raped, and request an HIV test. After pre-counselling, both mother and daughter consent to the test. The results come back – the doctor finds that the child is HIV-positive. However, she visits him alone and requests him not to make the result known to her mother, as she has been sexually active and the alleged rape did not take place.

The following questions arise in this scenario:

- What would be expected of a medical practitioner in terms of legal and ethical requirements?
- Would the situation be any different if the girl was 16 instead of 14?
- Should the doctor notify the Child Protection Unit, even if the sexual contact was consensual?
- How should the doctor handle a mother who insists on knowing the results?

1. The first principle is that a child of 14 years and older may, in terms of the Child Care Act of 1983, as amended, independently seek and obtain medical treatment (i.e. without parental consent). This includes an HIV test and its associated legal and ethical requirements (informed consent, counselling, confidentiality, etc.). When parent and child seek advice together, the medical practitioner should clarify this position and ask the child whether he or she is willing for the parent to be present. This would also give the opportunity to stress that the child has the right to confidentiality, and that the parent has no right to pressurise the medical practitioner to breach confidentiality. The decision to make the results of the test (or any medical treatment for that matter) known to the parent or any third party is in essence a matter to be decided between parent and child.

2. In this case it is clear that the patient wants this specific aspect of her medical information to be kept confidential. Ethically, a medical practitioner should respect this request. It is, however, imperative that she be advised on the effect

of her HIV status on others, possible treatment, and her responsibilities towards her sex partner(s) and her family (as a child who may get ill in future). By their very nature teenagers are not very 'rational' and it is recommended that she be referred for counselling from a person with special expertise in working with teenagers. (In this regard, see for example Van Dyk, *HIV/AIDS Care and Counselling*, chapter 9.<sup>1</sup>)

3. Sexual intercourse with a girl under the age of 16 has always been considered statutory rape in South Africa. However, legislation in this regard is about to change, partly in recognition of the fact that the reality in this country today is very different from the conditions under which the old sexual offences legislation was passed. What would the effect be if the practitioner in this case were to report the child's sexual behaviour to the mother? What would happen if the mother were to lay a charge of statutory rape at the local police station? Apart from the legal considerations there are also considerations of policy, ethics and health. Medical practitioners cannot cure society, but they can assist their patients in making wise health care decisions.

4. Medical practitioners have to report (suspected) child abuse. It is unlikely that consensual sex, especially between teenagers or young people, would be classified as child abuse. There is no statutory duty on health care professionals to report rape.

It is important to note that a new Children's Act, in which HIV testing of children is dealt with separately, is in the drafting phase. The draft suggests that in terms of consent to medical treatment, children aged 12 years and older, who are sufficiently mature and capable to understand the implications, risks and benefits of treatment, may consent to it. Children younger than 12 must be 'assisted' by a parent or caregiver. The medical fraternity should provide comment and input on this proposed legislation via their representative bodies.

1. Van Dyk A. *HIV/AIDS Care and Counselling. A Multi-Disciplinary Approach*. 2nd ed. Cape Town: Pearson Education, 2001.



## PROGRAMME MONITORING

# NATIONAL ANTIRETROVIRAL TREATMENT REGISTER — A NECESSITY?

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Highly active antiretroviral therapy (HAART) has greatly improved the prognosis of HIV-infected individuals in affluent countries, resulting in a marked drop in AIDS-related mortality.<sup>1-3</sup> In order to extend the benefits to resource-poor countries, the World Health Organisation (WHO) has called for expanded access to ART.<sup>4</sup>

### PERCEPTIONS OF SOUTHERN AFRICAN AND OTHER RESOURCE-POOR SETTINGS

A concern that widespread, unregulated access to antiretroviral (ARV) drugs in sub-Saharan Africa could lead to the rapid emergence of resistant viral strains, spelling doom for the individual, curtailing future treatment options, and leading to transmission of resistant virus, has been voiced.<sup>5</sup> This pessimistic perception of the outcome of HAART programmes in resource-poor settings is not inevitable, if a well-organised national treatment plan is developed.

Examples of highly successful ARV programmes in countries at a comparable stage of development to southern African countries, and with similar socioeconomic challenges, are the ARV (HAART) programmes incorporated into the Brazilian public health care system<sup>6</sup> and the pilot project instituted in rural Haiti, the poorest country in the Western hemisphere.<sup>7</sup>

### AFFORDABLE NATIONAL HAART PROGRAMME

In ongoing discussions surrounding the roll-out of ARVs by the state, cost is often mentioned as one of the 'problems'. In fact, a costing model of a rationed national HAART programme has recently been shown to be affordable within present South African budgetary constraints<sup>8</sup> and elements of civil society are now demanding increased access to HAART in the public health sector.<sup>9</sup>

With 360 000 estimated AIDS cases in South Africa<sup>10</sup> an ART

programme will need to be of a similar magnitude to that of the TB treatment programme and will face similar challenges as high levels of adherence to potentially toxic drugs are required for a prolonged period of time. The TB control programme utilises a standard two-scheduled approach to drug therapy, which simplifies the operational implementation necessary for a large national programme.

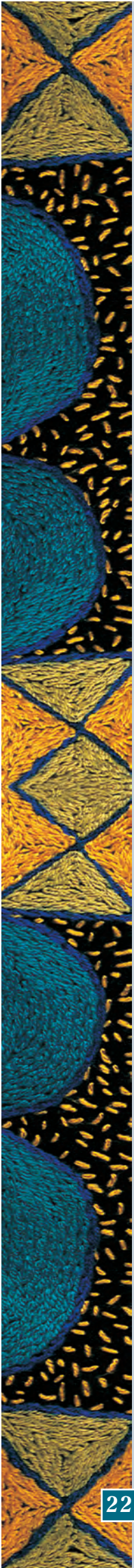
### ART TREATMENT REGISTER

The national TB register allows performance assessments to be made of individual clinics and ultimately the programme as a whole. Similarly, an ART scheduled approach would simplify training and education of medical personnel and would result in predictable patterns of toxicity and of resistance. A predetermined standardised sequence of drug combinations would also limit the number of drugs to be procured and managed.

There is an urgent need to establish a minimum data set required to allow evaluation and comparison of ARV projects in Africa.

A proposed register documenting entry criteria and recording ARV scheduled therapy would allow an overall audit of programme performance in a similar fashion to that of the TB register. Incorporation of the national ID number in conjunction with national death registration data would allow calculation of the survival of patients entering the programme on an 'intention to treat' basis (Fig. 1).

Comparison of these data with modelled survival of patients determined by baseline characteristics at entry to the programme would allow calculation of life-years gained by the programme. A national ART programme would utilise large quantities of relatively expensive drugs, and the financial burden of poor drug accountability could seriously undermine such a programme. The ARV treatment



Patient info		Baseline information		Schedule one (NNRTI based)		Changes within schedule 1		Schedule 2 (Protease inhibitor based)		Completion	
Reg No	1	WHO Clinical stage	1-4	Date started	11/07/01	Date	12/11/02	Date started		Date	
IMB		Staging diagnosis	1-20	A1 = AZT	B1 = NVP	Change 1	07/01/03	A1 = AZT	C1 = NFV	Change 1	
ID No		Date of diagnosis	11/10/02	A2 = 3TC	B2 = EFV	Change 2	04/23/03	A2 = 3TC	C2 = IND	Change 2	
ID No check		CD4 count	102	A3 = d4T	A6 = A2	Change 3		A3 = d4T	C3 = SQV	Change 3	
		Viral load	5.3	A4 = ddI		Change 4		A4 = ddI	C4 = AMP	Change 4	
				A5 = ddC		Change 5		A5 = ddC	D3 = IND/r	Change 5	
				A6 = ABC		Change 6		A6 = ABC	D4 = AMP/r	Change 6	
		Drug history	Naive	Current Therapy	3TC NVP	Reason for change		Current Therapy		Reason for change	
			MTCT	AZT	3TC	1 = intolerance		AZT	ddl	1 = intolerance	
			> 1 week			2 = laboratory toxicity				2 = laboratory toxicity	
						3 = viral failure				3 = failure	
						4 = other				4 = other	
						NB if virological failure proceed to schedule 2					
Reg No	2	WHO Clinical stage	1-4	Date started	11/07/01	Date	12/11/02	Date started	04/03/03	Date	
IMB		Staging diagnosis	1-20	A1 = AZT	B1 = NVP	Change 1	01/02/03	A1 = AZT	C1 = NFV	Change 1	
ID No		Date of diagnosis	11/07/01	A2 = 3TC	B2 = EFV	Change 2	04/03/03	A2 = 3TC	C2 = IND	Change 2	
ID No check		CD4 count	302	A3 = d4T	A6 = A2	Change 3		A3 = d4T	C3 = SQV	Change 3	
		Viral load	3.45	A4 = ddI		Change 4		A4 = ddI	C4 = AMP	Change 4	
				A5 = ddC		Change 5		A5 = ddC	D3 = IND/r	Change 5	
				A6 = ABC		Change 6		A6 = ABC	D4 = AMP/r	Change 6	
		Drug history	Naive	Current Therapy	ddl EFV	Reason for change		Current Therapy		Reason for change	
			MTCT			1 = intolerance		AZT	ddl	1 = intolerance	
			> 1 week			2 = laboratory toxicity				2 = laboratory toxicity	
						3 = viral failure				3 = failure	
						4 = other				4 = other	
						NB if virological failure proceed to schedule 2					
Reg No	3	WHO Clinical stage	1-4	Date started	11/07/01	Date	12/11/02	Date started		Date	
IMB		Staging diagnosis	1-20	A1 = AZT	B1 = NVP	Change 1	09/09/01	A1 = AZT	C1 = NFV	Change 1	
ID No		Date of diagnosis	09/09/01	A2 = 3TC	B2 = EFV	Change 2		A2 = 3TC	C2 = IND	Change 2	
ID No check		CD4 count	49	A3 = d4T	A6 = A2	Change 3		A3 = d4T	C3 = SQV	Change 3	
		Viral load	4.45	A4 = ddI		Change 4		A4 = ddI	C4 = AMP	Change 4	
				A5 = ddC		Change 5		A5 = ddC	D3 = IND/r	Change 5	
				A6 = ABC		Change 6		A6 = ABC	D4 = AMP/r	Change 6	
		Drug history	Naive	Current Therapy	3TC EFV	Reason for change		Current Therapy		Reason for change	
			MTCT			1 = intolerance		AZT	ddl	1 = intolerance	
			> 1 week			2 = laboratory toxicity				2 = laboratory toxicity	
						3 = viral failure				3 = failure	
						4 = other				4 = other	
						NB if virological failure proceed to schedule 2					
Reg No		WHO Clinical stage	1-4	Date started		Date	12/11/02	Date started		Date	
IMB		Staging diagnosis	1-20	A1 = AZT	B1 = NVP	Change 1		A1 = AZT	C1 = NFV	Change 1	
ID No		Date of diagnosis		A2 = 3TC	B2 = EFV	Change 2		A2 = 3TC	C2 = IND	Change 2	
ID No check		CD4 count	xxx	A3 = d4T	A6 = A2	Change 3		A3 = d4T	C3 = SQV	Change 3	
		Viral load	no	A4 = ddI		Change 4		A4 = ddI	C4 = AMP	Change 4	
				A5 = ddC		Change 5		A5 = ddC	D3 = IND/r	Change 5	
				A6 = ABC		Change 6		A6 = ABC	D4 = AMP/r	Change 6	
		Drug history	Naive	Current Therapy	ddl 3TC NVP	Reason for change		Current Therapy		Reason for change	
			MTCT			1 = intolerance		AZT	ddl	1 = intolerance	
			> 1 week			2 = laboratory toxicity				2 = laboratory toxicity	
						3 = viral failure				3 = failure	
						4 = other				4 = other	
						NB if virological failure proceed to schedule 2					

Fig. 1. Proposed web-based ART register.



register at any institution could be reconciled against drug purchases by that institution for drug accountability purposes and to identify and avoid 'drug seepage'. Specific questions such as impact of prior exposure to mother-to-child transmission preventive therapy on subsequent response to ART could be answered by analysis of the register database. Blood sampled at the time of failure of the first schedule could also be stored for national viral genotyping surveys, which could give information on patterns of viral resistance, which in turn would allow scientifically based changes in scheduled drug choices.

An ART register would need to be a standardised form that could be in either paper- or web-based formats. As ART will be provided at health care facilities other than TB clinics the administration of the register would need to be the responsibility of organisations such as the national or provincial AIDS directorates.

### OUTCOMES

The major outcomes of a successful ART programme would be a decrease in AIDS morbidity and mortality. While CD4 cell counts, clinical stage and viral load determine prognosis of untreated patients, effective viral suppression by ART is the major determinant of outcome on treatment.<sup>11</sup>

National and international ART guidelines have been developed and published, which give clear initiation criteria and recommended therapy combinations and could be used as a basis for scheduled drug choice.<sup>4,12</sup>

### LESSONS FROM THE TB CONTROL PROGRAMME

To encourage the correct usage of ART, it has been suggested that the ART programme be closely linked to and managed within the TB control programmes of sub-Saharan Africa.<sup>5</sup> ART cannot, however, be isolated from the wider comprehensive approach to HIV and AIDS patient care, including management of the psychosocial and other medical complications, such as prophylaxis and treatment of opportunistic infection.<sup>4,9</sup> It would not be practical or prudent to burden the TB control programme with this heavy responsibility. A scheduled ART approach could be a useful method to enable wider, more equitable access to ART within our existing health infrastructure, and an ART register would be a tool to monitor the overall performance of such an expanded access programme. While expanded access to ART should not be the responsibility of the TB clinics, there may be important lessons to be learned from the programmatic methodological approaches of the national TB control programme.

### PROTOCOL OUTLINE

The proposed register would be web-based with password-

protected access from registered PCs only. Entry of the individual national identity number would lead to an allocated site registration number, which would be used in all future communications. The proposed format of the register is shown in Fig. 1, and all data entry will be by 'point and click' menus. Baseline data will be entered including age, sex, WHO stage and staging conditions, baseline CD4 count and the initial treatment schedule chosen by the practitioner. Subsequent changes in treatment regimens would be categorised as due to toxicity, drug intolerance or viral failure together with dates of changes. The present drug regimen will be shown in an automatically updated regimen box.

Blood samples for genotyping will be stored at each change of therapy triggered by viral failure. Automatic e-mail requests for patient status will be generated to confirm whether subjects are still actively followed up or lost to follow-up. Funding has been sought to perform genotype-resistant pattern at the time of first failure of the second regimen. It is intended that these data be made available to the clinician for clinical decision-making.

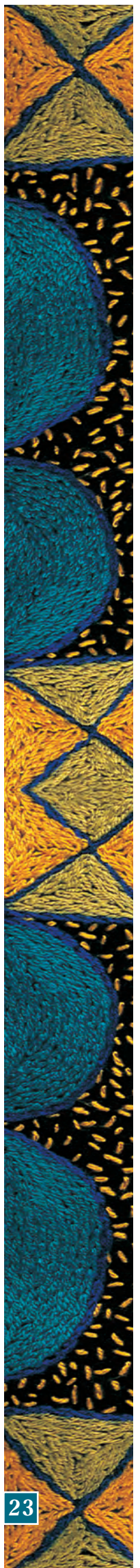
### REGISTER OUTPUTS

The register is intended to act as a pilot audit of current ARV clinical practice and to develop a tool for monitoring increasing widespread access to HAART. The primary aim is to assess the overall prognosis of subjects initiating HAART treatment in South Africa by establishing 'intention to treat' survival. Secondary endpoints include length of time on first non-nucleoside reverse transcriptase inhibitor (NNRTI)-based regimen in clinical practice, time to first virological failure and comparative tolerability of different starting regimens. Initial viral resistance genotype data will be made available for longitudinal population surveillance of circulating pre-treatment resistant mutations. Subsequent genotypic data will reflect viral response to present drug pressure and aid clinicians' therapeutic choices after failure of the protease inhibitor (PI)-based regimen.

### PARTICIPATION

It is envisaged that members of the SA HIV Clinicians Society who are experienced treaters participate in the programme by entering the password-protected Internet site from registered PCs. As indicated above, the entry of the individual national identity number would lead to an allocated site registration number, which would be used in all communications.

Participating medical practitioners would be required to recruit drug-naïve patients and be willing strictly to follow the current HIV Clinicians Society guidelines. The initial regimen would be an NNRTI-based regimen and the



subsequent or second-line regimen would be PI-based.

Any interested treaters who would like to participate should e-mail the managing editor of the *Southern African Journal of HIV Medicine* at [Igbekker@cormack.uct.ac.za](mailto:Igbekker@cormack.uct.ac.za), expressing the number of patients likely to be treated at their site in the next year.

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## GUIDELINES

# INFANT HIV DIAGNOSTIC GUIDELINES TO FACILITATE ADOPTION

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South Africa is currently estimated to have 300 000 HIV/AIDS orphans, and the figure is likely to increase to 2 million by 2015.<sup>1</sup> Facilitating adoption of children affected by HIV provides a highly effective strategy for addressing the HIV/AIDS orphan crisis, albeit on a very small scale. The legal and ethical issues surrounding HIV testing of abandoned children for the purposes of adoption are not addressed here.

The qualitative HIV polymerase chain reaction (PCR) test is highly specific for HIV infection, but sensitivity varies with the age of the infant.<sup>2</sup> The PCR identifies approximately 50% of infected infants at or just after birth and > 95% at 3 - 6 months of age.<sup>2,3</sup> More recent evidence suggests that HIV PCR tests performed at  $\geq 1$  month of age have a sensitivity of  $\geq 95\%$  and specificity of  $> 99\%$ .<sup>4</sup> The Roche Amplicor Kit (Roche Molecular Systems, Somerville, NJ)

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## HIV DIAGNOSTIC PROTOCOL FOR ADOPTION PURPOSES

### 6 weeks of age

HIV ELISA to assess HIV exposure at birth (omit if the HIV ELISA of the mother is confirmed positive)

Qualitative HIV PCR if the HIV ELISA of the infant (or the mother) is reactive

### 3 months of age

Qualitative HIV PCR to confirm result of PCR at 6 weeks of age

### Notes

1. **Clinical examination** to assess for stigmata of HIV infection should be performed at 6 weeks and 3 months of age. The 6-week clinical examination, when stigmata of HIV infection may be less evident, is likely to be less helpful than the 3-month examination.
2. At 6 weeks of age, blood should be taken for **both HIV ELISA and PCR** tests and the PCR analysed only if the HIV ELISA test result is reactive.
3. **Postnatal transmission** of HIV infection is likely to be evident by 6 weeks after termination of breast-feeding; nevertheless it is recommended that the final qualitative HIV PCR test be performed 3 months after breast-feeding has ceased.

### Interpretation

Two concordant qualitative HIV PCR results in an appropriate clinical context confirm the HIV status of the child. Discrepant PCR results require further investigation.

version 1.5, which has shown excellent sensitivity and specificity in the South African setting, is the recommended qualitative (DNA) PCR test.

There are no published HIV diagnostic guidelines for facilitating adoption. Such guidelines require a balance between making an **accurate** diagnosis of the child's HIV infection status and doing so as **early** in life as possible, factoring in practicalities and cost considerations.

Current HIV diagnostic guidelines for perinatally exposed infants recommend that HIV infection be confirmed by 2 positive HIV PCR tests performed on different samples. Negative HIV infection status is established if 2 HIV PCR tests, the first at  $\geq 1$  month of age and the second at  $\geq 4$  months, are negative in a non-breast-fed infant. To determine definitively that the child is not infected, seroreversion should be demonstrated by 2 negative HIV enzyme-linked immunosorbent assay (ELISA) tests, the final one performed at 24 months of age.<sup>3,5</sup>

The second PCR test is done to confirm the first PCR result and to guard against technical or sample mix-up errors. This could be achieved by re-testing as soon as possible after the first PCR test result is known,<sup>2,3</sup> but performing the second PCR at an older age increases the sensitivity of the test by detecting the  $< 5\%$  of infants who will test positive for the first time after 1 month of age. The recommended HIV diagnostic protocol for adoption purposes is explained in the box above.

The possibility that antiretroviral therapy used in prevention of mother-to-child transmission (PMTCT) programmes may affect the timing of the PCR testing in infancy has not been substantiated.<sup>4</sup> Local data on clinical stigmata of HIV at 6 weeks and 3 months of age and the sensitivity and specificity of qualitative HIV PCR as well as the influence of nevirapine for PMTCT on the timing of PCR testing are expected shortly. These diagnostic guidelines are likely to evolve as new data and technical improvements in testing become available.<sup>2</sup>

All abandoned neonates estimated to be  $\leq 72$  hours of age should be given post-exposure prophylaxis. If logistics are in place for obtaining HIV test results quickly, only HIV-exposed neonates should be treated.

It is theoretically possible for an HIV-exposed child to have a non-reactive HIV ELISA if the mother seroconverted late in pregnancy or, less plausibly, if she was terminally ill towards the end of the pregnancy. Both situations are associated with a high viral load and increased propensity for vertical transmission of HIV. The suggested diagnostic guidelines would not detect neonates exposed to HIV under these circumstances unless they presented with clinical stigmata. Despite the high prevalence of HIV in South Africa, it is expected to be rare for an HIV-exposed child to have a non-reactive HIV ELISA test, so qualitative HIV PCR testing of every child being investigated for adoption is not warranted.

Adoptive parents need to be aware of the fact that despite comprehensive general medical examinations and testing, there is no guarantee of a completely healthy child. In the context of HIV testing, this applies to the possibility of a negative HIV ELISA in an HIV-exposed child, as well as the recommendation to do the final HIV PCR test at 3 months instead of the exceptionally expensive and extreme recommendation of an HIV ELISA at 24 months of age.<sup>2,4,5</sup> Performing additional HIV tests is unlikely to yield different results from those achieved using the diagnostic guidelines suggested above.

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## PRESS RELEASE

### GlaxoSmithKline celebrates its centenary by sending 100 children to the STAR's Seaside Camp

What does a multinational company do to mark its 100 years of operation in South Africa? Hold a huge party for all its staff? Give the staff a special gift? Send a letter out to its customers? That's what most companies would do, but not pharmaceutical giant GlaxoSmithKline! When faced with the task of deciding how to commemorate the company's centenary in a memorable way, the GlaxoSmithKline management team, after considering many options, decided to send 100 underprivileged kids to camp!

The 100 lucky children, ages 10 to 12 years, come from Alexandra and thanks to GlaxoSmithKline spent ten fun-filled days at the STAR Seaside Camp in Durban from 12 to 21 February. For most it was their first sight of the sea and possibly their first time away from home on a holiday.

Members of the GlaxoSmithKline management team – Michael Spector, General Manager: Pharmaceuticals; Vicki

Ehrich, Director of Corporate Affairs; and Lorna Skhosana, Communications Manager – saw the children off. Said Spector: 'We are delighted to provide these youngsters with what I am sure will be the thrill of a lifetime. I cannot think of any more fitting way to commemorate our centenary.'

GlaxoSmithKline is no stranger to community involvement and support. Its corporate social investment budget is primarily aimed at helping South Africans to improve their quality of life with a focus on improved health for all. The company's philosophy is to achieve this by partnering with communities.

GlaxoSmithKline, which was formed two years ago by the merger of the former Glaxo Wellcome and SmithKline Beecham, is the fifth largest pharmaceutical company in South Africa and is well known for the many HIV/AIDS community initiatives it supports.



## LOOKING INTO THE MOUTH — ORAL MANIFESTATIONS OF HIV INFECTION (PART 3)

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Viruses are among the various microbiological agents responsible for manifestations of opportunistic infections observed in the oral cavity of individuals infected with the human immunodeficiency virus (HIV). Opportunistic viral infections occur in all three of the groups of lesions associated with HIV infection, according to the European Commission-World Health Organisation (EC-WHO) classification.<sup>1</sup>

**Group I.** Lesions strongly associated with HIV infection.

- Kaposi's sarcoma (KS)

**Group II.** Lesions less commonly associated with HIV infection

- Herpes simplex virus (HSV)
- Human papillomavirus (HPV) (wart-like lesions)
  - Condyloma acuminatum
  - Focal epithelial hyperplasia
  - Verruca vulgaris
- Varicella-zoster virus (VZV)
  - Herpes zoster
  - Varicella

**Group III.** Lesions seen in HIV infection

- Cytomegalovirus (CMV)
- Molluscum contagiosum

Any one of several different viruses may infect the mucosa of the oral cavity, and each produces a relatively distinct clinicopathological picture, hence the necessity for a working **clinical classification of viral diseases affecting the oral mucosa.**

**1. Vesiculo-bullous lesions (result in secondary ulcers)**

- HSV infection (herpes simplex 1 and 2)
- VZV infection (varicella-zoster virus)
- Hand-foot-and-mouth disease (Coxsackie A virus strains)
- Herpangina (Coxsackie type A viruses: A1-6, A8, A10, A22 and B3)
- Measles (rubeola) (measles virus)

**2. Ulceration without preceding vesicle formation**

- CMV

**3. Exophytic lesions**

- Verruca vulgaris (HPV – many subtypes)
- Focal epithelial hyperplasia (Heck's disease) (HPV subtypes 13 and possibly 32)
- Condyloma acuminatum (HPV A6 and A11)
- Hairy leukoplakia (HL) (Epstein-Barr virus)
- KS (human herpesvirus 8)
- Burkitt's lymphoma (Epstein-Barr virus)

**4. Swellings**

- Mumps parotitis (CMV)

### HERPES SIMPLEX VIRUS INFECTIONS

HSV infections usually produce vesicular eruptions of the skin and oral mucosa, and occur in two forms: (i) the acute primary disease, which has both local and systemic manifestations; and (ii) the secondary disease, which is localised, confined mainly to the vermilion border of the lips and the surrounding skin, and without any accompanying systemic symptoms.

**Primary herpetic gingivostomatitis** usually affects children, adolescents or adults younger than 25 years, or adults who have failed to produce an appropriate response to a previous infection. It is usually caused by HSV-1, and to a much lesser extent by HSV-2, usually secondary to orogenital contact. The lesions caused by the two viruses are indistinguishable clinically. The incubation period after exposure ranges between 2 and 14 days. The primary lesions are numerous fragile vesicles that often coalesce and rupture early, producing numerous painful irregular ulcers; they may be observed on any mucosal surface, the vermilion border of the lips or the skin around the lips. The gingiva become inflamed, swollen and extremely erythematous. The primary lesions are accompanied by fever and malaise resembling the prodrome of influenza, complaints of pain, headache, loss of appetite, and often swollen and tender cervical lymph nodes.

The primary systemic infection lasts for between 7 and 12 days, and the vesiculo-ulcerative lesions heal without any

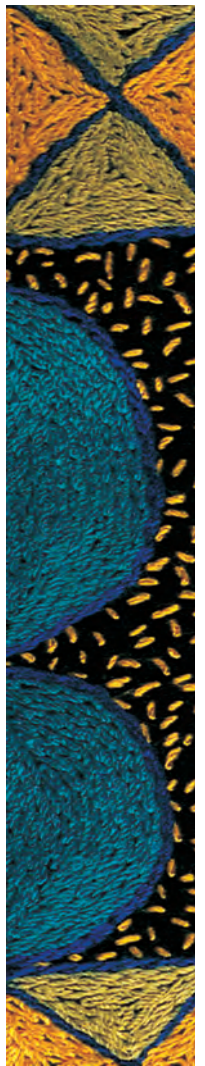
scarring. By this time the virus has migrated to the trigeminal nerve ganglion, remaining there in a latent form.

In **secondary or recurrent HSV infection** two major clinical presentations are seen, i.e. recurrent herpes labialis and recurrent palatal herpes, representing reactivation of the latent virus. Reactivation is stimulated by trauma to tissues innervated by nerves of latently infected ganglion cell bodies,<sup>2</sup> upper respiratory infections, ultraviolet light irradiation, menstruation, emotional stress, and immunosuppression. Whether or not reinfection takes place in a seropositive individual from an exogenous source is still a matter for debate. The lesions are usually confined to the hard palate and the gingiva, although they may present on the dorsal surface of the tongue, in contrast to the primary form of the disease, in which lesions occur on any oral mucosal surface. A very large proportion of the population have already produced antibodies to HSV, and less than half of this group will develop secondary herpes disease. Just before the appearance of the lesions the patient usually experiences prodromal symptoms of tingling, burning or pain at the site in which the vesicles will appear. The vesicles break down, become ulcerated and coalesce, forming superficial ulcers that become crust-covered, healing within 7 to 12 days without scarring. Each

recurrence typically occurs at or near the same site regularly. The number of recurrences an unfortunate patient will experience is variable and ranges from one per year to as many as one per month. In my experience I had seen only a few cases of recurrent primary herpetic gingivostomatitis before the advent of HIV infection.

**The diagnosis** of primary herpetic gingivostomatitis is largely apparent from the clinical features, but can be confirmed by a viral culture, which requires several days for positive identification, by serological samples taken over 2 weeks and showing a rising titre of antibodies to HSV, or by taking a smear of fluid from a fresh vesicle which will show numerous virus-infected multinucleated epithelial cells (ballooning degeneration). These cytological features will also be seen in fresh fluid from secondary/recurrent herpes vesicles, but the antibody titres to HSV remain constant.

In HIV-positive immunocompromised individuals, both intraoral and genital recurrent HSV lesions are frequent and particularly troublesome. The prevalence of intraoral herpes infection among HIV seropositive groups ranges from 5% to 13%.<sup>3</sup> The presentation of herpetic stomatitis is somewhat different from the classic form of herpetic gingivostomatitis (especially in AIDS), and the clinical



## ADVERT



course is dramatically altered. The lesions are much more severe and extensive, occurring in atypical patterns; for example, clustered vesicles and ulcers may involve the entire hard palate, the lower labial mucosa, or buccal mucosa unilaterally.<sup>4</sup> The labial lesions progress rapidly and result in diffuse weeping ulcers that extend onto the facial skin and persist for many weeks or even months. Recurrent herpes labialis may be found to coexist with perianal ulcerative herpes simplex, and HSV-2 can often be isolated from both sites among homosexual men.

**Treatment.** For any drug to be effective timing is the most important factor; it must be administered as soon as possible, not later than 48 hours from onset of symptoms generally being regarded as ideal. Topical acyclovir is not effective in treating intraoral lesions, and may not be effective in treating herpes labialis. At present no single therapeutic regimen has been shown to be uniformly effective in the treatment of oral HSV infection.

### VARICELLA-ZOSTER VIRUS INFECTIONS

The VZV is one of the herpesviruses that is pathogenic for humans, being responsible for the primary infection chickenpox (varicella), which is predominantly a childhood disease, and for herpes zoster (shingles), which is its reactivation syndrome. VZV has many striking similarities to HSV. Just two, which relate to pathogenesis, are that VZV has the ability to remain quiescent in sensory ganglia for indefinite periods after a primary infection, and that a cutaneous or mucosal vesiculo-ulcerative eruption following reactivation of the latent virus is typical of both HSV and VZV. Herpes zoster mainly affects the older adult population, and also immunocompromised individuals including kidney transplant recipients, patients with leukaemia undergoing chemotherapy, patients receiving high-dose radiation or steroids, and patients with HIV infection, who are all prone to this expression of recurrent VZV disease.

### CHICKENPOX

Most individuals have been exposed to VZV in childhood, so chickenpox is very rarely associated with HIV infection, although an early case was reported of a 42-year-old homosexual man who experienced a severe attack of chickenpox with extensive cutaneous and oral manifestations, which responded well within 2 weeks to acyclovir treatment.<sup>5</sup>

A relatively common finding in perinatal AIDS is chronic persistent VZV infection. Widespread cutaneous lesions develop, persist for many weeks, and predispose to secondary bacterial infection; however, none of the published reports mention any oral manifestations in these

infants.<sup>6</sup> With oral acyclovir therapy some of these paediatric patients later develop resistance, while others show acyclovir-resistant strains from inception.<sup>7</sup>

### HERPES-ZOSTER VIRUS INFECTION

Secondary infection (zoster) is one of the earlier clinical signs of HIV infection, especially in young adults under the age of 35; these patients will have a 23% chance of developing AIDS 2 years and a 46% chance 4 years after the diagnosis of zoster.<sup>8</sup> The annual incidence of zoster in the general population is about 0.14%, but the rate among HIV-infected persons is increased sevenfold.<sup>9</sup>

The diagnosis of herpes zoster is based on the symptoms of pain and the distinctive, usually unilateral, vesicular eruption corresponding to the area innervated by one or more branches of the trigeminal or other sensory nerve. As the virus infects the sensory nerve of a dermatome prodromal symptoms of pain or paraesthesiae develop and persist for several days. Prodromal complaints may include pain referred to teeth that are quite healthy. This presents a problem for the clinician when the trigeminal nerve is involved in a patient complaining of toothache occurring in the maxillary premolar area, and later in the mandibular premolar area, and all the teeth are vital and intact. Often because of incorrect diagnosis a tooth or teeth are extracted or endodontically treated. Four to five days later, a vesicular eruption is observed in the preauricular area extraorally and on the mandibular gingiva extending to the retromolar trigone.

In HIV-infected patients the clinical course is more severe. An eruption of vesicles develops, they become pustular and eventually ulceration follows. The lesions often persist much longer, lasting for several weeks, and in about 10% of patients troublesome post-herpetic neuralgia may develop, taking several months to resolve. Occasionally local cutaneous hyperpigmentation may also be noted; this persists long after healing of the zoster lesions, and when seen in an adult under the age of 35 provides the clinician with evidence of previous zoster infection, indicating the possibility that the patient is harbouring HIV infection.

### ORAL HAIRY LEUKOPLAKIA

Cases of oral HL were first noted in San Francisco in 1981 among homosexual men and first described by Greenspan and co-workers in 1984.<sup>10</sup> Since then this lesion has been seen in HIV-infected individuals in all risk groups worldwide. It has mainly been observed in immunocompromised persons, almost exclusively those with HIV infection, though occasionally it has been seen in other categories of immunosuppressed patients such as organ and bone marrow transplant recipients.<sup>11,12</sup> HL is not

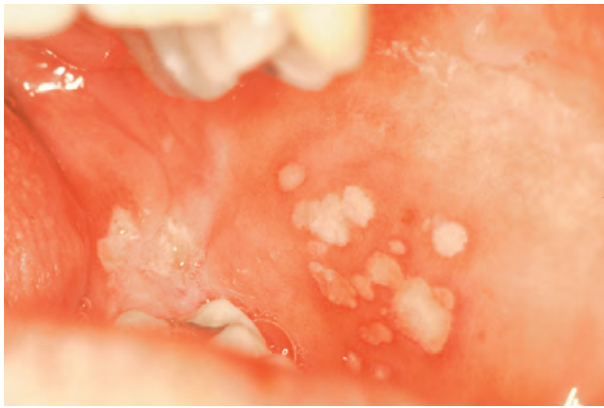


Fig. 1. Primary herpetic gingivostomatitis – collapsed coalesced vesicles on buccal mucosa forming secondary ulcers.



Fig. 4. Secondary herpes labialis – crop of vesicles at angle of mouth.

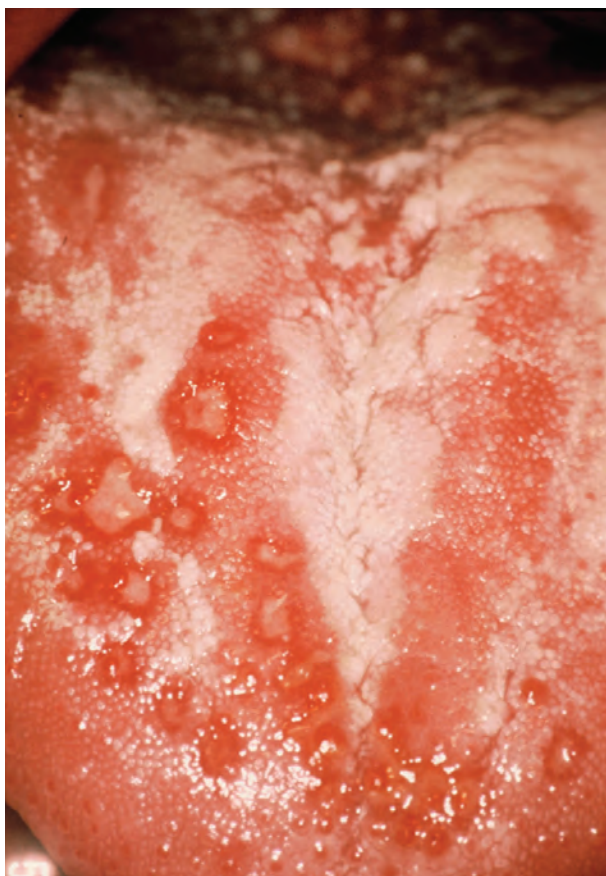


Fig. 2. Confluent secondary ulcers on dorsum of tongue, interspersed with super-infection with *Candida* organisms.

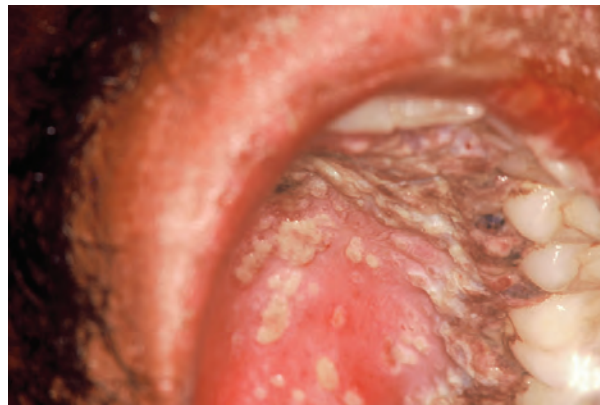


Fig. 5. Herpes zoster infection in a 28-year-old man, affecting the left half of the hard palate.



Fig. 3. Inflamed erythematous swollen lower gingiva.



Fig. 6. The same patient as in Fig. 5, about 3 days after symptomatic treatment with chlorhexidine 0.2% mouth rinse.





absolutely specific for HIV infection, but is rather a manifestation of chronic severe immunosuppression and appears to be a predictor of poor prognosis. Its presence in HIV-seropositive individuals more often than not indicates a fairly rapid progression to AIDS in the absence of antiretroviral drugs.<sup>13</sup>

HL, a white adherent keratotic lesion, caused by epithelial hyperplasia, commonly occurs on the lateral borders of the tongue, either unilaterally or bilaterally. It is characterised by a flat or slightly raised, poorly demarcated area, varying from very small patches a few millimeters in size, to several

patches that run together, or may even be so extensive as to completely cover the dorsal surface and part of the ventral surface of the tongue. Very often there are characteristic vertical striations, giving it a corrugated or 'hairy' surface. Uncommonly, HL occurs in other oral sites, namely the buccal and lower labial musosa, oropharynx, palate and floor of the mouth.

Clinically it may be difficult to distinguish HL from other white lesions of the tongue, such as idiopathic leukoplakia, frictional keratosis (tongue chewing), tobacco-associated leukoplakia, and chronic hyperplastic candidosis; other less common entities are lichen planus, lupus erythematosus, and possibly the keratotic reaction associated with electrochemical interactions.

The lesion is usually asymptomatic, although patients may sometimes complain of mild roughness and express concern about the appearance, so specific treatment is rarely indicated. Although these lesions are frequently superinfected with *Candida* species they are not of any aetiological importance, because HL does not resolve with antifungal therapy. Epstein-Barr virus has been shown to be present in the epithelial cells of HL, and is thought to be involved in its pathogenesis, as the lesion completely disappears after treatment with high doses of acyclovir.<sup>14</sup>

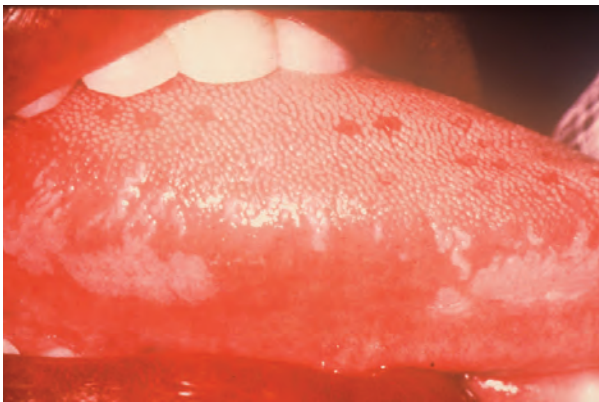


Fig. 7. Hairy leukoplakia showing plaques and a few vertical folds.

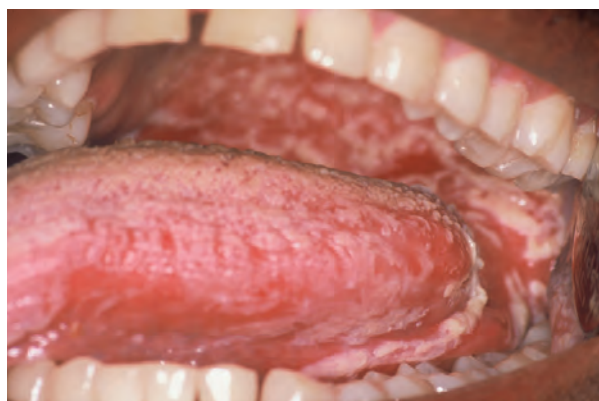


Fig. 8. Hairy leukoplakia – extensive, also pseudomembranous and hyperplastic candidosis.



Fig. 10. Kaposi's sarcoma, hard palate – nodular exophytic tumour right side and slightly raised lesion left side; pseudomembranous candidosis present.



Fig. 9. Kaposi's sarcoma – flat and slightly raised lesions on soft palate.

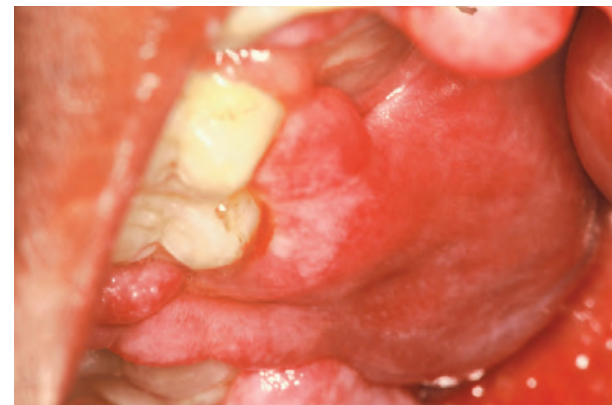


Fig. 11. Kaposi's sarcoma – extensive lesion involving whole of hard palate.

## KAPOSI'S SARCOMA

The oral KS lesion at the early stage may present as a rather trivial-appearing flat patch, a red-purple or blue-purple discolouration on the oral mucosa, which does not blanch with pressure. In the later stages the lesion becomes progressively raised, and increases to a rather ominous nodular exophytic tumour, for example, involving the entire hard palate. It may be solitary or multiple. As the lesions become progressively larger they often ulcerate, usually due to trauma, and the individual may experience bleeding and/or pain.

KS may present anywhere in the mouth, but the most commonly involved sites are the hard and soft palate, followed by the gingiva and to a lesser extent the tongue. It is the most frequently found malignancy in the developed world, but figures for the prevalence of oral KS in the southern African countries are lacking. KS has been found to be significantly more common in patients with lower CD4 counts, and increased in prevalence over the follow-up period, demonstrating that it is associated with advanced immune suppression and increases with progression of disease.<sup>15</sup> KS is one of the indicator diseases for AIDS, as defined by the CDC.<sup>16</sup>

The most likely transmissible agent causing KS is the  $\gamma$ -herpes virus, KSHV<sup>17</sup> or HHV8.<sup>18</sup> Boshoff and co-workers have detected sequences by polymerase chain reaction (PCR) in each of the epidemiological types of KS, namely, HIV+ve AIDS, HIV-ve classic, HIV-ve post-transplant, HIV-ve gay men, and HIV-ve African endemic.<sup>19</sup> At present there is no curative therapy for KS, and a lack of comparative studies of different treatment modalities and treatment of oral lesions, to guide the clinician, so management has to be directed at control and palliation, relief of pain, and attention to functional and cosmetic factors. Treatment is extremely important for psychological reasons owing to the continuing stigmatisation of AIDS. Intraoral treatment is necessary when lesions interfere with function and the ability to maintain an adequate state of oral hygiene. Treatment modalities for epidemic KS may be divided into several groups, namely: (i) local measures; (ii) interferon- $\alpha$  (INF $\alpha$ ); (iii) cytotoxic chemotherapeutic agents; (iv) low-dose radiation; and (v) now highly active antiretroviral therapy (HAART). The differential diagnosis of KS must include haemangioma, erythroplakia, melanoma and a remarkable look-alike known as bacillary angiomatosis that mimics KS both clinically and microscopically. The diagnosis of oral KS can easily be confirmed by incisional biopsy under local anaesthetic.

## HUMAN PAPILLOMAVIRUS INFECTION

HPV is an epitheliotropic DNA virus, with more than 60 genotypically distinct subtypes that cause disease in

human beings. **Oral squamous papilloma** is used as a generic term to include papillary and verrucal growths composed of benign epithelium and minor amounts of supporting connective tissue. HPV-induced lesions occurring in the mouth in association with HIV infection include verruca vulgaris (infective warts), condyloma acuminatum and focal epithelial hyperplasia (Heck's disease). All these lesions are associated with several different HPV types.

**Verruca vulgaris** lesions may be on any intraoral site, especially the hard and the soft palate, where they are generally solitary, although on occasions numerous lesions may be noted. Generally they measure less than 1 cm, appearing as exophytic granular to cauliflower-like surface alterations, and are asymptomatic. The treatment of choice is surgical excision or laser ablation.

**Condyloma acuminatum** is characteristically located in the anogenital region and to a lesser extent may involve the oral mucosa. It is primarily a sexually transmitted disease, and has been seen with increasing frequency in HIV-infected patients. The lesions appear as either small, solitary wart-like papillomas or multiple flat broad-based lesions. Treatment is generally surgical excision, including cryosurgery, electrocautery, or laser ablation.

**Focal epithelial hyperplasia** (Heck's disease) is characterised by numerous nodular soft-tissue masses present on all mucosal surfaces, particularly the labial mucosa, the buccal mucosa, the tongue and to a lesser extent the gingiva, or appearing as discrete or clustered papules similar in colour to the surrounding mucosa. These lesions have been seen in our oral medicine clinic, predominantly in young children who are HIV-seronegative, and very occasionally in adults, who have all been HIV-seropositive. Widespread involvement of the mucosa usually occurs, but no particular treatment is necessary other than to reassure the young patient's worried mother. Spontaneous regression has been observed in many of our cases.

## CYTOMEGALOVIRUS

Oral involvement by CMV is rare, but when infection of the oral tissues occurs, large, sharply demarcated oval ulcers without rolled margins, often multiple and painful, are usually seen. They may easily be mistaken for recurrent minor aphthous ulcers.

## MOLLUSCUM CONTAGIOSUM

Molluscum contagiosum is a common viral skin disease caused by a member of the Poxviridae group, presenting as discrete white/skin-coloured, umbilicated papules. The lesions are predominantly found on the neck, trunk, eyelids



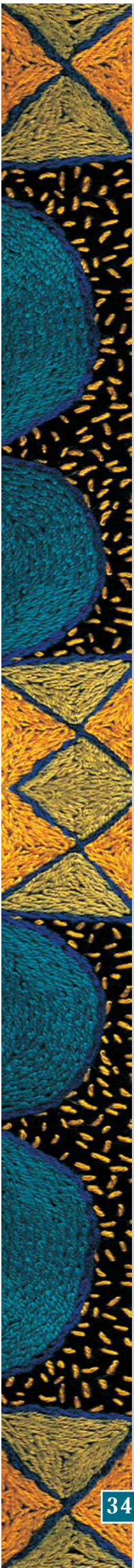


Fig. 12. Kaposi's sarcoma – extensive lesion involving anterior half of tongue.



Fig. 15. Condyloma acuminatum in 32-year-old-man.



Fig. 16. Focal epithelial hyperplasia lesions on lower labial mucosa.



Fig. 13. Kaposi's sarcoma simulating drug-induced gingival enlargement in a 24-year-old pregnant woman.



Fig. 17. Focal epithelial hyperplasia, mainly on anterior part of tongue.



Fig. 14. Verruca vulgaris at junction of hard and soft palate.



Fig. 18. Cytomegalovirus ulcer on lower labial mucosa.

and anogenital area, and occasionally on the vermilion border of the lips.

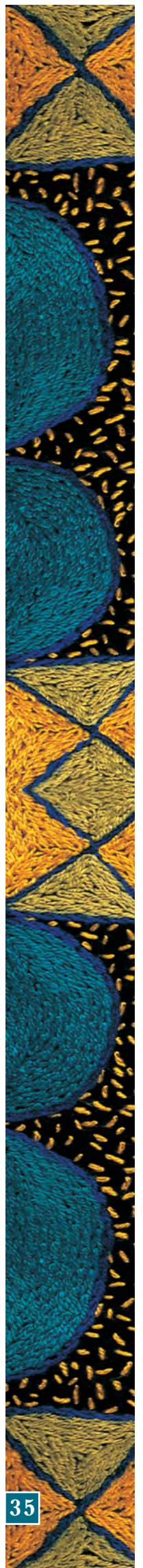
### HIV IN ORAL TISSUES

The oral mucosa is frequently exposed to the infectious human immunodeficiency virus. Despite this, transmission by the oral route is rare. The virus has been identified in saliva and normal tissues including salivary lymphocytes, and obtained from fibroblast cells of the dental pulp, yet it has not been involved in the initiation of any specific oral lesions.<sup>20</sup> Several mechanisms for limiting HIV transmission through the oral route have been suggested, namely: (i) HIV immunoglobulins; (ii) endogenous innate factors; or (iii) the virtual absence of intact infectious viral particles. Saliva contains several antiviral factors that naturally hinder viral infection through the oral route. Among these, secretory leukocyte proteinase inhibitor (SLPI) has been proposed to be the only saliva-derived protein that possesses anti-HIV activity at physiological levels.<sup>21</sup>

All clinical photographs were taken by the departmental photographer, Mrs Sophie Mokubedi, and the photograph of condyloma acuminatum is reproduced with permission from Professor J-C Petit.

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## VACCINE UPDATE

# CONDUCTING HIV VACCINE TRIALS — CHALLENGES FOR SOUTH AFRICA

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South Africa is experiencing a severe HIV/AIDS epidemic. It is estimated that at least 1 in 10 South Africans are HIV-infected, and data from the 2001 antenatal seroprevalence survey suggest that at least 1 in 4 pregnant women are HIV-infected (South African Department of Health). To date, despite the introduction of national prevention programmes there is no sound evidence that the epidemic is reaching a plateau. It has been estimated that HIV infection rates will peak at almost 17% by 2006 for the population as a whole. AIDS-related deaths will peak in 2010, at 256 AIDS deaths per 100 non-AIDS-related deaths.<sup>1</sup>

Several risk factors in South Africa predispose it to a severe epidemic. These include a disrupted family and communal life, due in particular to apartheid and migrant labour; good transport infrastructure and high mobility; high levels of poverty and income disparity; evidence of high levels of sexually transmitted diseases; poor condom use; the low status of women in society and relationships; and social norms that accept large numbers of sexual partners. As mass awareness programmes and prevention strategies that focus on behaviour change have not curbed the epidemic, there is an urgent need to investigate biomedical approaches to HIV prevention. The initiation of an HIV-vaccine-related research programme in South Africa presents many challenges to scientists working in this field.

### CHALLENGES FACING HIV VACCINE RESEARCH

As yet, South Africa has not been involved in HIV vaccine clinical trials. The challenges facing researchers in South Africa are not unique, but are barriers similar to those seen in other developing world settings.

These include:

#### REGULATORY ISSUES

There is an urgent need to build local regulatory capacity to review vaccine trials. At present swift in-country review and the approval process appears to be hampered by inexperience. Between December 2001 and November 2002, three phase I/II trials were submitted for regulatory

approval to the South African Medicines Control Council (MCC). Despite discussions between the MCC, investigators, sponsors and the South African AIDS Vaccine Initiative (SAAVI), no trial had been approved during this time. After submission of the first HIV vaccine trial, the MCC mandated a new committee to deal with HIV vaccine trials, the HIV Vaccines and Clinical Trials Committee, which has to report to the MCC meeting before final approval. Initial questions and responses from the MCC to vaccine trial investigators have taken between 3 and 18 months. The review by the HIV Vaccine and Clinical Trials Committee was not only scientific and regulatory, but also included review of biomedical ethical issues and the commitment of researchers to capacity development of previously disadvantaged communities. The HIV Vaccine and Clinical Trials Committee wanted assurances of access to lifelong highly active antiretroviral therapy (HAART) before approval could be given for the first HIV vaccine trial, submitted in December 2001. Although the time between submission and review was lengthy, investigators were often expected to respond within the standard 7 days of receipt of the review, often without being able to access committee members via phone or fax for clarifications. In the first quarter of 2003, the MCC together with the National Department of Health convened a meeting with the National Ethics Committee to gain consensus on appropriate standard of care for volunteers who become infected on HIV vaccine trials. There was overwhelming agreement that access to antiretrovirals was an important component to the standard of care for trial participants who became infected on these trials.

#### ETHICAL REVIEW

The government has not made HAART available in the state or private sector for the management of HIV-infected individuals who meet treatment criteria. Because of the lack of access to HAART in the public sector, there was no consensus in this country regarding the treatment and management of participants who may have 'breakthrough' infections while on vaccine trials. While investigators subscribe to the UNAIDS ethical considerations in HIV preventive vaccine research (2000) (guidance point 16:

where care and treatment for HIV/AIDS should be provided to participants in HIV vaccine trials, with the ideal to provide the best proven therapy, and the minimum to provide the highest level of care attainable in the host country), there is lack of clarity regarding who is responsible for this care.

Attempts to obtain a consensus on the use of antiretroviral therapy for 'breakthrough' infections held up ethical clearance of HIV vaccine trials. Since the national meeting where it was determined that there will be access to antiretroviral therapy for trial participants who have 'breakthrough' infections while on the trial, the universities have now given approval for the phase I/II HIV vaccine trials that have been submitted to them.

### CROSS-CLADE HIV VACCINE TRIALS

The variability of HIV-1 poses a major challenge to the development of an HIV vaccine. There is controversy among scientists in this country regarding the value or importance of cross-clade vaccine research. Trials should be designed to evaluate whether candidate vaccines are capable of inducing potent and broad cellular immune responses to HIV. Because of the increasing diversity of the HIV epidemic globally, with increasing frequency of recombinant forms, the development and testing of clade-specific vaccines in regions may not be the appropriate route to take. In South Africa, approximately 94% of the predominantly heterosexual epidemic is due to clade C, while 85% of the minority homosexual epidemic is attributed to clade B.<sup>2</sup> There are as yet limited data regarding recombinant forms in South Africa, but as the epidemic evolves, more mixing of clades can be expected, resulting in recombinant forms of HIV-1. There are published reports suggesting that cross-clade reactivity can be induced by natural infection, but homologous responses are frequently greater than heterologous responses.<sup>3-6</sup>

Other ways of addressing diversity issues can include multivalent cocktails of proteins that comprise a spectrum of regional variants with the assumption that the immune responses elicited by any one of the circulating strain will be of sufficient cross-reactivity to protect against other strains from the same subtype.<sup>7</sup>

### ADOLESCENT INVOLVEMENT

One of the most effective ways to curb the epidemic will be to vaccinate older children and adolescents prior to their sexual debut, particularly in South Africa where 50% of 15-year-olds and almost 10% of under-12-year-olds are sexually experienced. The use of an HIV vaccine in this population will require clinical trials in adolescents to determine the vaccine's safety and immunogenicity as the Food and Drug Administration (FDA) and international licensing agencies will probably only license the vaccine for

use in age groups in which it has been tested. Generally, candidate HIV vaccines have been studied in phase I/II trials in healthy adult volunteers. To date, no HIV vaccines have been evaluated in adolescents.

There are challenges researchers need to overcome to successfully complete HIV vaccine trials in adolescents, and because of this, adolescents are often excluded from clinical research. Treatments and interventions used in this group are usually extrapolated from studies performed in children or adults.<sup>8</sup> Many national committees and panels have recognised the lack of research involving adolescents, and have urged that more research be conducted in this age group.

South Africa needs a clear strategy to involve adolescents in vaccine trials. Ethical issues regarding informed consent, consultation with parents and HIV testing of minors need to be addressed in an expedient manner.

### ESTABLISHMENT OF HIV VACCINE CLINICAL SITES

Disparities exist between urban and rural health care and 'local standards of care' differ dramatically. In rural areas, the doctor/patient ratio is lower than in urban areas, where patients may only access rotating medical doctors at a primary health care level once a week. Access to drugs on the essential drug list may be sporadic, and there are concerns that in rural areas where trial sites are being developed, better access to medical care may act as a perverse incentive for clinical trial participation. In a survey conducted in Soweto, an urban African setting on the outskirts of Johannesburg, almost 70% of participants stated that they would definitely participate in HIV vaccine research. Access to HIV testing, risk reduction counselling and condoms, and treatment of sexually transmitted diseases were cited as reasons to be involved in HIV vaccine clinical trials. In this survey, only 36% of participants believed that HAART should be provided to trial volunteers who had breakthrough infections.

### TRAINING OF RESEARCHERS

Clinical researchers need to be trained adequately so that all trials conducted in South Africa are in accordance with the International Conference on Harmonisation of Good Clinical Practice (ICH GCP) and the highest ethical standards. In South Africa there are currently few researchers trained in ICH GCP and able to conduct trials under Federal Drug Administration (FDA) scrutiny. In addition, there are no concrete plans in South Africa to develop sufficient phase III capability to allow the testing of suitable vaccine candidates in phase III clinical trials. There is a paucity of black African scientists involved in HIV research, and in particular HIV vaccine research, in South Africa. To this end, the academic institutions involved in HIV vaccine research have committed themselves to the





development of scientists from previously disadvantaged communities and prioritised the training of both clinical and laboratory scientists.

### PROTECTING TRIAL PARTICIPANTS

South Africa is uncharted territory in terms of HIV vaccine clinical research. HIV vaccine trials to be conducted in South Africa will largely involve people from populations which, through limited knowledge about science and research, advanced poverty, unemployment and gender inequality, may be vulnerable to exploitation and manipulation by research programmes. Trial participants deserve protection from social harm or any form of discrimination that may arise from their participation in HIV vaccine research.

It is therefore apparent that South Africa needs to work on legislation that will ensure the protection of trial participants from any form of harm arising from participating in HIV vaccine research. Some units within South Africa have built up considerable skills, infrastructure and approaches to HIV clinical trials. These will be fundamental to designing and carrying out successful vaccine trials in communities, which in the process will be enabled to become research-literate and empowered partners.

### INVOLVING COMMUNITIES

Public dialogue, education and outreach are essential for successful HIV vaccine research and this process has not been systematic in South Africa. There is a need to embrace communities involved in research in a meaningful and constructive way. One way of achieving this is by the establishment of democratically elected and truly representative community advisory boards (CABs). Regular contact and communication between the CAB and researchers will open up channels of dialogue necessary to facilitate the successful execution of clinical trials.

### VACCINE ACCESS

Strategies must be developed now to ensure that after being licensed the HIV vaccine is readily available to all sectors of the population.

### SUMMARY

Although many steps are necessary for the successful implementation of HIV vaccine clinical research, most of the infrastructure and expertise exists in this country. To expedite the approval and initiation of the first phase I/II trials in South Africa, it is apparent that local regulatory capacity necessary for research and licensure needs to be developed as a matter of urgency. An important issue that threatened the initiation of HIV vaccine research pertained

to 'standards of care', and what this constitutes in a country with no provision of HAART in the public sector. Although this has been resolved at a policy level, it is apparent that clinical researchers, together with local institutional review boards and the national Department of Health, will need to develop a model of care for participants who acquire 'breakthrough' infections while participating in vaccine trials. This model will need to encompass the challenges of long-term follow-up, monitoring and care, including expertise in treating with HAART and ensuring an uninterrupted supply of antiretroviral drugs. The national Department of Health will need to take the lead in establishing the national guidelines on 'standards of care' and to provide the infrastructure and treatment necessary for long-term follow-up and care for trial participants who seroconvert on trials. SAAVI must continue to identify and develop phase III clinical trial sites both in rural and urban areas, preferably as soon as the phase I/II trials commence. As the appropriate target group for vaccination will be adolescents before their sexual debut, a strategy for testing of HIV vaccines in adolescents needs to be fast-tracked in the region. Finally, once an efficacious vaccine has been tested, a plan for the urgent procurement and distribution is needed to make this vaccine available to all South Africans as quickly as possible.

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## VACCINE UPDATE

# THE INFRASTRUCTURE SUPPORTING HIV VACCINE CLINICAL TRIALS

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### BACKGROUND

History has shown that vaccines have provided the key to epidemic disease control. It is imperative, however, that vaccination is integrated into effective public health programmes. These include life skills education, sanitation, potable water supply, environmental and other health care and service provision.

Current interventions have failed to sustain control in the spread of the HIV epidemic. A preventive HIV vaccine is considered the best hope of curbing the epidemic, and considerable international and national resources are being directed to this end. This has resulted in an alignment of these resources into two main coherent international networks, namely the HIV Vaccine Trials Network (HVTN – [www.hvtn.org](http://www.hvtn.org)) and the International AIDS Vaccine Initiative (IAVI – [www.iavi.org](http://www.iavi.org)). Their core aim is to accelerate the production of a safe, effective and affordable preventive HIV vaccine. The South African AIDS Vaccine Initiative (SAAVI – [www.saavi.org](http://www.saavi.org)) is a vital contributor to and partner in both these collaborations.

The infrastructure developed in this quest so far is both impressive and complex. It is structured to harness the considerable intellectual input and investments required to achieve the goal of an effective HIV vaccine in the shortest possible time.

This article describes the infrastructure in global, national and site or regional levels. It concentrates mainly on the HVTN network at an international level and on SAAVI at a national level. Information on IAVI can be accessed via the Internet address given above.

### GLOBAL

The HVTN is based in Seattle in Washington, USA. Its operations comprise a core operations centre, a statistical and data management centre, central laboratories, a community advisory board co-ordinating directorate, and HIV vaccine clinical trial units. Linkages have been established at various levels including the National Institutes of Health (NIH), the National Institute of Allergy



and Infectious Diseases (NIAID), the Division of AIDS (DAIDS), the US Food and Drug Administration (FDA), the Office of Human Research and Protection (OHRP), the US Walter Reid Army Institute for Research, vaccine developers, biotechnology companies, the pharmaceutical industry, universities and research institutions.

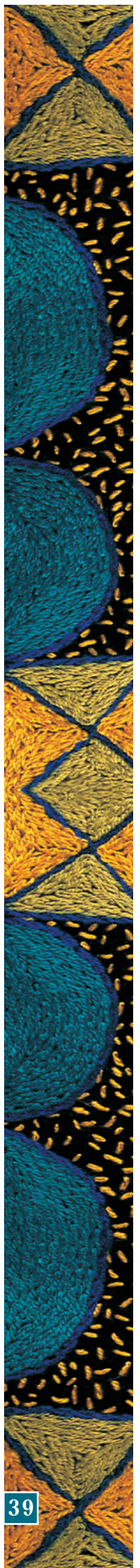
The HVTN co-ordinates its activities through a number of committees and task teams including a scientific steering committee, scientific committees covering the various phases of clinical trials (phases I, II and III) and laboratory sciences. Working groups or teams address development, protocols, primary infections, paediatrics and adolescents, and non-human primates.

This operation is co-ordinated by various mechanisms such as biannual HVTN full group meetings, conference calls, etc. in a standardised manner guided by the HVTN's Manual of Operations (MOP).

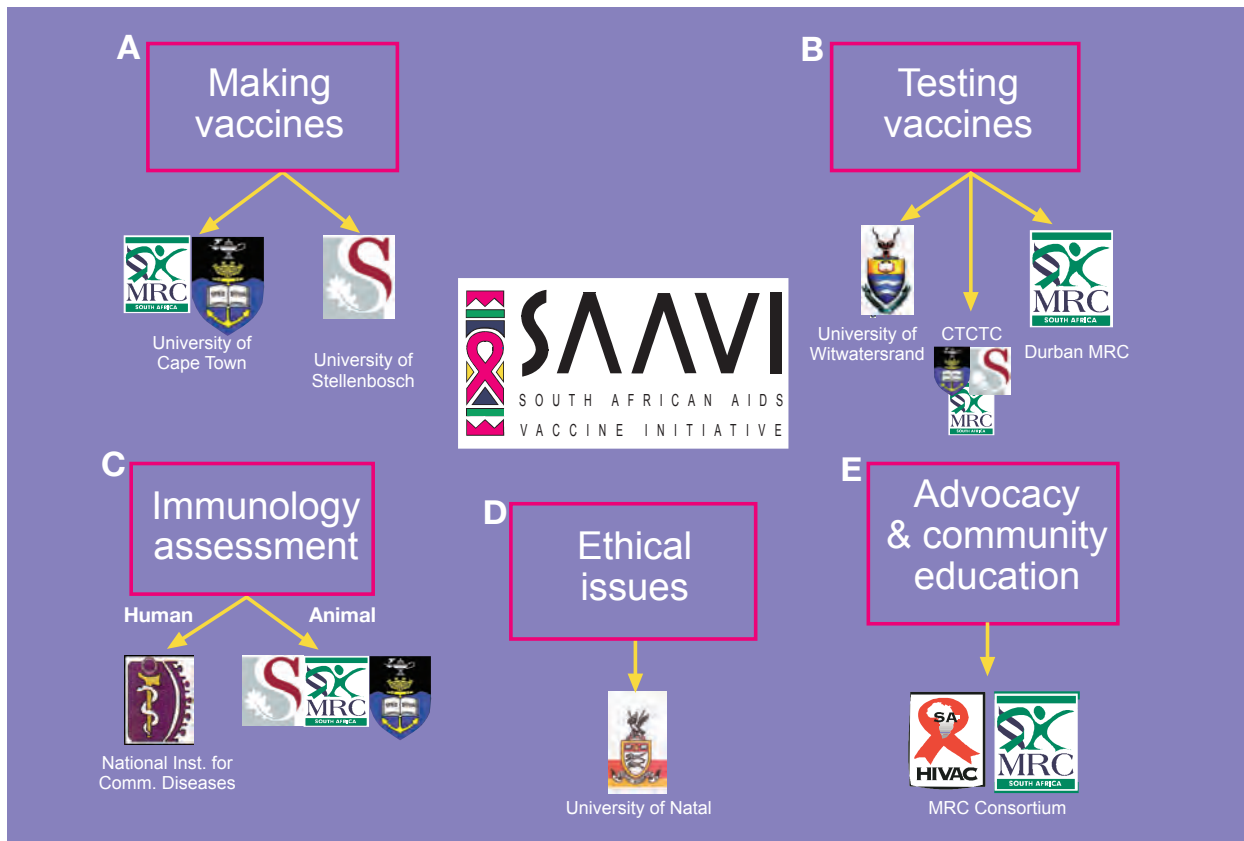
### NATIONAL

The South African AIDS Vaccine Initiative (SAAVI) was formed by Cabinet in 1999 to co-ordinate the research, development and testing of HIV vaccines in South Africa. SAAVI is based at the South African Medical Research Council (MRC) and is an integral player in the international networks. It is funded by the South African Government and Eskom, and also by the NIH, the European Union and other international organisations.

SAAVI is a broad-based community research entity which co-ordinates vaccine research and development work at







various South African academic institutes such as

- the National Institute of Communicable Diseases (NICD), which will examine and track the immune responses to HIV/AIDS test vaccines
- research teams based at the universities of Cape Town and Stellenbosch that are aiming to develop new test vaccines and track the prevalence of circulating HIV strains
- an HIV/AIDS Vaccines Ethics Group (HAVEG) at the University of Natal
- the South African HIV Vaccine Action Campaign (SA HIVAC), which is a consortium focusing on community education, legal and human rights, as well as media and communications
- a behavioural sciences group
- a primate research centre, and
- established clinical trial sites at the Perinatal HIV Research Unit at Chris Hani-Baragwanath Hospital in Soweto and at the MRC in Durban, as well as two additional sites to be developed in Cape Town and Orkney.

#### REGIONAL CLINICAL TRIAL UNITS

This vast infrastructure is geared to enable the clinical trial sites to timeously enrol volunteer participants and undertake clinical trials of suitable candidate HIV vaccines. These units are geared to generate data of high quality to answer the necessary research questions in the quest for a safe, affordable and effective vaccine.

These sites have many similarities with other clinical research facilities. They require staffing, facilities and equipment necessary to meet the exacting internationally accepted requirements demanded of HIV vaccine research, the ethical care and management of volunteer participants, and meaningful community integration in all these processes.

#### STAFF

The staff complement at these sites consists of the principal investigator (PI), co-investigators, research clinicians, pharmacists, laboratory technicians, nurses, data managers, administrators, HIV/AIDS counsellors, social scientists, community outreach personnel such as educators, liaison officers and recruiters, and quality assurance personnel. These units are usually supported by information technology, financial, security and cleaning staff. The staffing operation must be aligned to real capacity building with the aim of meeting employment equity legislative requirements.

All personnel need to have training, or be trained and continually updated in the various aspects of clinical research such as good clinical practice (GCP), the numerous (50+) standard operating procedures (SOPs), MOPs and protocol-specific requirements. Ongoing training aims to enable them to meet their varied responsibilities within the highly complex, sensitive arena of HIV clinical research. In addition, frontline staff require media training to ensure that a coherent, clear and co-ordinated message necessary for such an undertaking is communicated to the public.

The PIs are responsible for the quality and integrity of the conduct of vaccine clinical trials, the medical care of participants to the highest ethical standards, protocol conduct with the agreed approvals by the Medicines Control Council (MCC) and the various ethics committees, and also the provision of quality staffing, facilities and equipment.

The PI's responsibilities to this end encompass submission of protocol and amendments to the regulatory authorities and adherence to the requirements of these regulatory authorities with confidential data management and transmission, and document storage. They are also responsible for the education, recruitment, enrolment and retention of participants, which encompasses a functional community advisory board (CAB) and other community mobilisation and education activities. Units also typically establish in-house voluntary counselling and testing (VCT) services which add to the recruitment process. The PIs ensure compliance with the International Committee of Harmonisation (ICH) GCP guidelines for the medical management and monitoring of participants, vaccine management such as cold-chain maintenance, storage, reconstitution and administration, and specimen collection in adherence to protocol, and sponsor policy and procedures. They must also ensure that specimen collection processing and shipment meets the requirements of the International Air Transport Association (IATA).

The PI is also responsible for the establishment, facilitation and maintenance of CABs, which are required to reduce the perceived power imbalance between researchers, participants and communities. These CABs comprise community representatives, and usually include representation from community-based organisations (CBOs), non-governmental organisations (NGOs), traditional leaders and practitioners, faith-based organisations, trade unions and governmental departments, among others. CABs require training to enable them to input meaningfully to the clinical trial process such as the informed consent process, inclusion/exclusion criteria, participant care, and recruitment and retention issues.

These CABs are organised and co-ordinated internationally in a highly structured way and exert a powerful influence in ensuring appropriate, expedited HIV vaccine research.

### FACILITIES AND EQUIPMENT

Vaccine trial sites typically comprise examination rooms supported by an emergency care facility, pharmacy and laboratory, waiting and counselling areas, offices, secure document storage rooms and freezer repositories.

Standard equipment includes IT equipment and networking, telephones and fax, photocopiers, scanners, etc., as in most clinical trial units. In addition a pharmacy equipped with fume extraction cupboards for safe vaccine reconstitution, and -40°C freezers with temperature controls, alarms, and logs to ensure continual temperature controls is also required. An electrical back-up generator is required to ensure uninterrupted power to run the freezers. This is linked to a service company to ensure 24-hour functionality.

The site laboratories are equipped and staffed mainly for specimen preparation such as serum separation, peripheral blood mononuclear cell (PBMC) isolation, specimen shipment and tracking, test result management, and on-site rapid testing such as pregnancy and HIV tests.

### LINKAGES

Clinical trial units, apart from their links with international and national HIV vaccine groups, communicate with many organisations, institutions and people within the region in which they operate. These include the government Departments of Health at central, provincial and local spheres, ethics committees, hospitals (both private and state), clinics and GPs, CBOs, NGOs, faith-based organisations, the media and trade unions.

### CONCLUSION

This is an overview rather than an exhaustive description of the fine detail which, of necessity, exists right down to the needle tip or device delivering the HIV vaccine. These minutiae, however, are all essential to ensure that the correctly modified HIV antigenic fragments are delivered safely and expeditiously into volunteer participants and that all outcomes are managed appropriately.

Never before has a global endeavour of this magnitude and intricacy been mounted in the search for a vaccine. The development of the polio and smallpox vaccines was not supported by a mustering of this intensity. We should remind ourselves of the time it took to control smallpox – from Dr Jenner's inoculation of Master James Phipps in the 1760s to its eventual eradication in the 1970s – not forgetting the vaccination activities predating this. By contrast, some modern vaccines have been developed in only a few decades.

Is this complicated infrastructure sufficient in terms of quality, magnitude, courage and will to produce a safe, effective and affordable preventive HIV vaccine within the next decade? We hope so – but until such time, the public health education, care and treatment programmes must rise to meet the need.



# DYSLIPIDAEMIA AND LIPODYSTROPHY ASSOCIATED WITH HIV INFECTION AND ANTIRETROVIRAL THERAPY

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Approximately 4.8 million South Africans are currently infected with the human immunodeficiency virus (HIV) and most are likely to die of AIDS-related illnesses. Prevention of new infections through educational efforts, mother-to-child programmes and development of an HIV vaccine is a key component in managing the HIV epidemic. Patients with symptomatic HIV infection should be treated with antiretroviral therapy (ART).<sup>1</sup>

Effective ART dramatically reduces the mortality and morbidity associated with AIDS.<sup>2-4</sup> Current ART does not cure HIV infection but suppresses viral replication. ART is lifelong and the number of patients taking antiretroviral drugs is steadily increasing, as is the number of antiretroviral drugs available. As mortality associated with HIV-related opportunistic infections declines, drug-related toxicity is being increasingly recognised and researched. ART is associated with a wide variety of potential adverse effects. The development of a lipodystrophy syndrome has generated particular research interest and concern among HIV clinicians and patients.

### LIPODYSTROPHY SYNDROME

Lipodystrophy in patients receiving ART was first described in 1998.<sup>5-7</sup> The lipodystrophy syndrome describes a complex constellation of altered fat distribution, dyslipidaemia and insulin resistance. Whether this is a single disease entity with variable manifestations or the various aspects of this syndrome represent differing pathologies is still controversial. Both the severity and scope of the lipodystrophy syndrome may vary considerably between patients.

### FAT REDISTRIBUTION

Adipocytes respond variably to the introduction to ART, with peripheral (mainly subcutaneous) adipocytes reacting differently to central (visceral) adipocytes. Peripheral lipoatrophy (loss of fat from the face, limbs and buttocks) occurs if there is excessive apoptosis of peripheral

adipocytes, while excessive storage of triglycerides in visceral adipocytes causes central fat accumulation. Lipoatrophy in severely affected patients results in a gaunt face with sunken cheeks and thin spindly limbs with prominent veins and muscles. Fat accumulation causes an abdominal paunch ('Crixivan belly') in addition to breast hypertrophy and a 'buffalo hump'. Preliminary results of a recent study suggest that lipoatrophy is HIV-specific, while lipohypertrophy may be linked to age-related central obesity and the contrast between peripheral fat loss and central fat preservation.<sup>8</sup> Morphological changes do not remit spontaneously and may be progressive.<sup>9</sup>

### DYSLIPIDAEMIA

HIV infection itself is associated with dyslipidaemia, with lipid metabolism becoming increasingly deranged as immune deficiency progresses.<sup>10-12</sup> High-density lipoprotein (HDL) cholesterol falls early in HIV infection, while moderate hypertriglyceridaemia and decreased low-density lipoprotein (LDL) cholesterol are characteristic of advanced immunodeficiency. Other chronic infections are associated with similar lipid disturbances and these relate to increased levels of tumour necrosis factor  $\alpha$  (TNF $\alpha$ ) and interferon- $\alpha$  (INF $\alpha$ ).<sup>12-14</sup>

Dyslipidaemia in patients on ART is not dependent on viral suppression, CD4 count or weight gain achieved<sup>15</sup> and therefore is not related to immune reconstitution. HIV-negative volunteers treated with ritonavir for 2 weeks developed dyslipidaemia,<sup>16</sup> indicating that some antiretroviral drugs cause dyslipidaemia directly.

Dyslipidaemia has been best characterised in patients receiving protease inhibitor (PI) drugs. In patients receiving ritonavir, total cholesterol increased by a mean of 2.0 mmol/l (mean cholesterol on treatment 6.6 mmol/l) while triglycerides increased by 1.8 mmol/l (mean triglyceride on treatment 3.64 mmol/l). Lipoprotein (a) levels increased by 48% in patients with baseline levels of more than 20 mg/dl.<sup>17</sup> HDL cholesterol remains unchanged

or may decrease moderately with ART. Small very-low-density lipoprotein (VLDL) and intermediate-density lipoprotein (IDL) particles are increased, while LDL particles tend to be small and dense.<sup>18,19</sup> The combination of small dense particles with increased remnants of triglyceride-rich lipoproteins (IDL) is generally regarded as highly atherogenic<sup>20</sup> and resembles the lipid phenotype characteristic of the metabolic syndrome.

### INSULIN RESISTANCE

Insulin resistance in patients on ART is characterised by abnormalities in multiple metabolic pathways.<sup>21</sup> Insulin fails to suppress endogenous glucose production and lipolysis, while peripheral glucose uptake and metabolism is reduced.<sup>21</sup> In insulin-resistant patients euglycaemia is maintained at the expense of high circulating insulin levels. Impaired glucose tolerance and subsequently diabetes develop when pancreatic insulin secretion fails.

### THE MAGNITUDE OF THE PROBLEM

Estimates regarding the incidence and prevalence of lipodystrophy vary widely as there is no universally accepted definition or set of diagnostic criteria. Fat redistribution can be assessed by patient or physician reporting, dual energy X-ray absorption (DEXA) or full-body magnetic resonance imaging (MRI). Insulin resistance can be measured directly by clamp techniques (labour intensive) or indirectly by fasting proinsulin, C-peptide or a fasting insulin/glucose ratio (HOMA index).<sup>22</sup> Further variability is introduced by differences in the demographics of patients studied and the variable nature and duration of the ART given. Recently parameters for monitoring fat redistribution and metabolic function in trials of antiretroviral medication have been proposed.<sup>23</sup>

In a recent review of 1 035 patients receiving ART, dyslipidaemia or fat maldistribution was found in 50% of all subjects. The prevalence of peripheral wasting was 36%, abdominal weight gain was seen in 33% of patients, and a 'buffalo hump' was noted in 6%. Dyslipidaemia was found in 22% of these patients,<sup>24</sup> while other series have reported dyslipidaemia in more than 70% of patients.<sup>9</sup> Diabetes was diagnosed in 7% of patients on PI-based ART after oral glucose tolerance testing (GTT), while the fasting glucose was diagnostic of diabetes in only 2% of the study patients.<sup>9</sup> New-onset hyperglycaemia (defined as a random serum glucose level of more than 7.8 mmol/l on two or more occasions) was reported in 5% of patients.<sup>15</sup>

### PATHOPHYSIOLOGY

The pathophysiology of the lipodystrophy syndrome(s) remains incompletely understood. Although ART is implicated in most cases, there are HIV-infected patients

naïve to ART with lipodystrophic features. Lipodystrophy is not dependent on HIV viral load<sup>9</sup> and can occur when ART is given for primary HIV infection.<sup>25</sup> All antiretroviral agents have been associated with lipodystrophy, although PI therapy is particularly strongly associated with morphological alterations and hypertriglyceridaemia. A higher incidence of lipoatrophy has been reported with stavudine therapy.<sup>26-29</sup>

ART may cause lipodystrophy by interfering with cellular regulatory mechanisms. The metabolic response to ART is very variable, however, indicating that environmental (e.g. diet, exercise) and genetic factors influence the ultimate phenotype.

In 1998 Carr *et al.*<sup>30</sup> proposed that lipodystrophy may be the consequence of PI-mediated inhibition of two human proteins, cytoplasmic retinoic-acid binding protein type 1 (CRABP-1) and LDL receptor-related protein (LRP). This hypothesis has subsequently not been supported by experimental evidence.<sup>31-33</sup>

PIs may cause hyperlipidaemia by their inhibitory action on the human 26S proteasome.<sup>34</sup> Secretion of apolipoprotein B (apoB)-containing lipoproteins from the liver is partially regulated by degradation of newly synthesised apoB in the proteasome.<sup>35</sup> PI-mediated inhibition of proteasomal function results in increased secretion of apoB-containing lipoproteins from hepatocytes in the presence of sufficient neutral lipid.<sup>36</sup>

Sterol regulatory element-binding protein-1c (SREBP-1c) is a transcription factor that increases sterol and triglyceride content of cells by upregulating transcription of the LDL receptor gene and genes for key enzymes in sterol and triglyceride synthesis. Overexpression of SREBP-1c results in increased lipid synthesis, which is not metabolically compensated for by increased LDL receptor expression. Ritonavir results in nuclear accumulation of SREBP-1c in mice by inhibiting proteasomal degradation of SREBP-1c.<sup>37</sup> Indinavir inhibits SREBP-1c-dependent genes in cell culture.<sup>38,39</sup> These discrepant results could be related to the variety of cell and animal models studied. The different PIs studied may also have divergent effects. In humans undergoing plastic surgery for lipoatrophy, SREBP-1c protein levels were elevated 2.6-fold in subcutaneous abdominal tissue.<sup>40</sup>

Transgenic mice overexpressing active SREBP-1c constitutively develop severe lipodystrophy, insulin resistance and hypoleptinaemia.<sup>41</sup> Leptin deficiency is linked to insulin resistance as leptin therapy reverses insulin resistance in hypoleptinaemic transgenic mice<sup>42</sup> and in humans with congenital lipodystrophy<sup>43</sup> who also have very low leptin levels.



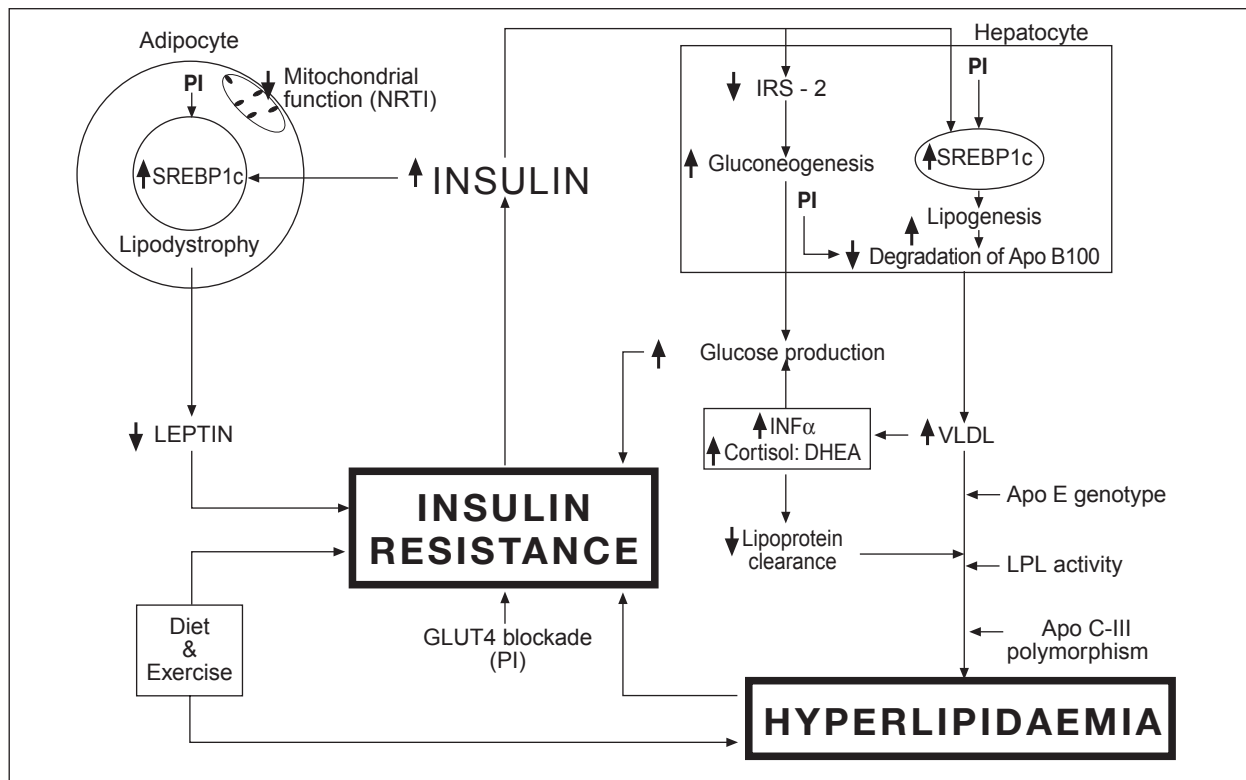


Fig. 1. Cellular changes associated with antiretroviral therapy. The diagram presents a possible explanation for some of the features of the lipodystrophy syndrome. Protease inhibitors (PI) increase the concentration of sterol regulatory element-binding protein-1c (SREBP-1c) in both adipocytes and hepatocytes. Lipid synthesis is increased in hepatocytes, while degradation of nascent apoB100 is inhibited. More very-low-density lipoproteins (VLDL) are secreted, resulting in hyperlipidaemia, which is modulated by apoE genotype, lipoprotein lipase activity (LPL) and polymorphisms in apoCIII. Accumulation of SREBP-1c in adipocytes leads to lipodystrophy and decreased leptin levels. Nucleoside reverse transcriptase inhibitor (NRTI)-induced mitochondrial toxicity may also contribute to lipodystrophy. Low levels of leptin are associated with insulin resistance, while increased insulin levels contribute to increased SREBP-1c levels, establishing a vicious cycle. Increased insulin levels also downregulate insulin receptor substrate (IRS2), leading to less suppression of gluconeogenesis. PIs also cause direct insulin resistance by blockade of GLUT4. The ultimate phenotype is influenced by environmental factors such as diet and exercise as well as other ill-understood genetic influences.

The severity of ART-induced hyperlipidaemia is further modulated by apolipoprotein E genotype,<sup>44</sup> lipoprotein lipase activity<sup>45</sup> and polymorphisms in the apolipoprotein-CIII gene.<sup>46</sup>

Increased levels of  $\text{INF}\alpha$ <sup>47</sup> and an increased cortisol/dehydroepiandrosterone (DHEA) ratio<sup>48</sup> have been found in patients with lipodystrophy and may contribute to hyperlipidaemia and insulin resistance.

Nucleoside analogues (NRTIs) could cause lipodystrophy through mitochondrial toxicity.<sup>49,50</sup> NRTIs not only inhibit viral reverse transcriptase but also have an inhibitory effect on DNA polymerase- $\gamma$ , the enzyme responsible for transcribing mitochondrial DNA (mtDNA). Many of the side-effects of NRTIs (e.g. myopathy, lactic acidosis) are explained by mitochondrial toxicity, but there is no solid evidence as yet that lipodystrophy results from mitochondrial toxicity.<sup>51,52</sup>

CD36 is a sterol scavenger receptor and promotes the accumulation of lipids in macrophages and the formation of atherosclerotic lesions.<sup>53,54</sup> PIs induce a specific increase in macrophage CD36 expression, and this promotes

accumulation of cholesteryl ester in macrophages and atherosclerosis.<sup>55</sup> This effect was seen even with PIs that do not cause hyperlipidaemia or at doses not associated with hyperlipidaemia.

PIs acutely and at therapeutic concentrations selectively inhibit GLUT4,<sup>56,57</sup> an insulin-regulated glucose transporter. Inhibition of GLUT4 causes insulin resistance by decreasing insulin-mediated peripheral glucose disposal. Phosphorylation of glucose in skeletal muscle is reduced in patients with lipodystrophy,<sup>58</sup> further decreasing insulin-mediated glucose disposal. Speculatively mitochondrial dysfunction may impair hexokinase activity by limiting the amount of adenosine triphosphate (ATP) available for formation of glucose-6-phosphate.

#### CLINICAL IMPLICATIONS

Lipodystrophy and lipohypertrophy can be very distressing and may adversely affect compliance with ART, resulting in virological failure and an increased risk of resistance. There is increasing concern about the potential impact of dyslipidaemia and insulin resistance (or overt diabetes in

some patients) on cardiovascular morbidity and mortality. Activation of CD36 by PIs could further increase the atherosclerotic risk. The final verdict on the atherogenic potential of ART still awaits the results of several large prospective cohort studies. However, there are case reports<sup>59,60</sup> of premature ischaemic heart disease in patients on ART and some retrospective studies suggest an increased risk.<sup>61</sup> Studies assessing secondary endpoints in ART-treated patients also demonstrate endothelial dysfunction<sup>18</sup> and increased plaque formation in the carotid arteries.<sup>62</sup> Severe hypertriglyceridaemia may cause pancreatitis, and lipaemic plasma always has serious implications and should alert the doctor to the risk of pancreatitis.

### MANAGEMENT ISSUES

No evidence-based management strategies are currently available, although data are accumulating rapidly.<sup>63</sup> It seems reasonable to ascertain baseline metabolic values and family history of diabetes and cardiovascular disease in patients about to commence ART. This information may influence the selection of an initial regimen along with other factors such as virological efficacy and cost. For instance, patients with pre-existing hypertriglyceridaemia should avoid ritonavir with its propensity to cause hypertriglyceridaemia,<sup>17</sup> while nevirapine-based regimens (no PI) have been associated with a potentially protective elevation of HDL cholesterol.<sup>64</sup>

Lifestyle modification and general cardiovascular risk reduction are recommended for all patients on ART. Patients should be encouraged to stop smoking, optimise their weight and exercise regularly, and should follow a prudent diet.

Subsequent to lifestyle modification there are two main strategies to consider in patients with lipodystrophy. One may attempt to modify the antiretroviral regimen to decrease toxicity, a 'switch strategy', or additional drugs

may be used to treat the metabolic problems. Either strategy requires a thorough knowledge of antiretroviral therapeutics and possible drug interactions.<sup>65</sup> When contemplating a switch strategy the patient's current virological control, previous treatment exposure and the risk of new treatment-related toxicities should be taken into consideration. Generally PI-based therapy has been switched to non-nucleoside reverse transcriptase inhibitor (NNRTI)-based therapy (nevirapine or efavirenz) or abacavir (an NRTI) has been used. Hyperlipidaemia often improves when PI therapy is withdrawn, but the effects of PI withdrawal on insulin resistance and fat distribution are less consistent.<sup>66</sup>

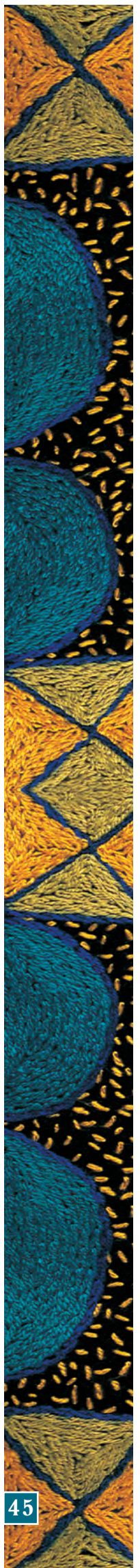
Investigational approaches to fat maldistribution include growth hormone therapy,<sup>67</sup> anabolic steroids<sup>68</sup> and plastic surgery (liposuction, fat implantation), although the effect of the latter may only be temporary.<sup>69</sup> Metformin therapy improves insulin sensitivity<sup>70</sup> and glitazones may be beneficial as well.

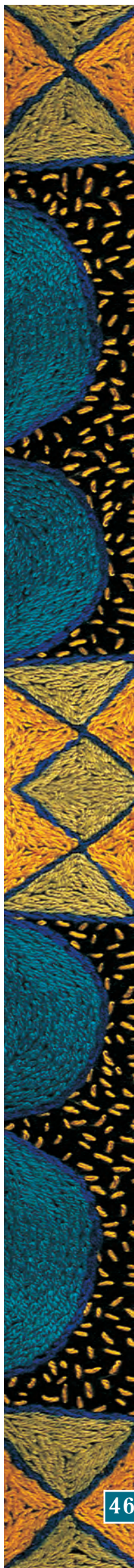
Preliminary guidelines for the management of dyslipidaemia have been published.<sup>63,71</sup> Current recommendations are to follow national guidelines for the evaluation and management of dyslipidaemia in the general population. These guidelines emphasise lifestyle modification and a global cardiovascular risk assessment. If lipid-lowering drugs are necessary (Table I) fibrates should be used when there is predominant hypertriglyceridaemia. Fibrates have been well tolerated in clinical trials and there seems to be little difference in efficacy between the various fibrates.<sup>72</sup> Statins are given for hypercholesterolaemia and significant drug interactions can occur as most PIs inhibit CYP3A4, which also metabolises many statins. Pravastatin and atorvastatin are least affected, with pravastatin area under the curve (AUC) decreasing by 50%, atorvastatin AUC increasing by 79% and simvastatin AUC increasing by more than 3 000%<sup>73</sup> in HIV-negative volunteers treated with ritonavir or saquinavir. Lovastatin would be expected to show a similar response to simvastatin. Pravastatin and

TABLE I. DRUG THERAPY FOR DYSLIPIDAEMIA ASSOCIATED WITH ART

Lipid phenotype	First-line therapy	Second-line therapy	Comments
Predominant hypertriglyceridaemia	Fibrate (any agent)	Consider changing ART* Nicotinic acid <sup>†</sup> , statin	Pancreatitis may occur, very-low-fat diet (< 30 g fat/day) essential Medical emergency
Predominant hypercholesterolaemia	Statin (atorvastatin or pravastatin)	Nicotinic acid <sup>†</sup> , fibrate	Initiate statin at low dose, titrate slowly, cholestyramine may significantly interfere with absorption of ART
Mixed hyperlipidaemia	Fibrate or statin	Consider combination of statin and fibrate, nicotinic acid	Increased risk of myopathy with combination therapy

Lipid-modifying drugs should generally not be initiated before adequate lifestyle modification and a formal assessment of cardiovascular risk. Many patients will not require drug therapy. Extreme derangement of lipid metabolism (especially severe hypertriglyceridaemia) may require simultaneous initiation of lifestyle modification and drug therapy. Changing ART may improve dyslipidaemia, but should not compromise virological efficiency and may be associated with new side-effects or drug interactions.  
\* Severe hypertriglyceridaemia not responsive to fibrates may necessitate discontinuation of PI therapy.  
† Nicotinic acid can cause insulin resistance and is therefore not first-line therapy.





atorvastatin can therefore be used under careful supervision. Statins should be initiated at low doses (pravastatin 20 mg/d or atorvastatin 10 mg/d) and the patient should be informed about potential adverse effects (especially on the muscles) and monitored closely.

## CONCLUSION

The lipodystrophy syndrome(s) continue(s) to challenge researchers and clinicians and the literature in this field is expanding rapidly. Awareness of the metabolic complications of ART is of particular importance in South Africa, where there is a high prevalence of genetic hyperlipidaemias, which may be exacerbated by ART. Familial hypercholesterolaemia (FH) is highly prevalent (up to 1:100) in the Afrikaner, Jewish and Indian population groups in South Africa owing to local founder effects.<sup>74</sup> Genetic hyperlipidaemia is also encountered in the black population<sup>75</sup> and dysbetalipoproteinaemia may have an increased prevalence.<sup>76</sup> Obesity, hypertension and diabetes are also prevalent in South Africa and may interact negatively with ART. Future research needs to be targeted at antiretroviral drugs that more specifically inhibit viral proteins without disrupting human cellular function. In the future we may also be able to predict, by means of genetic testing, the likelihood of adverse effects in a specific patient and select drugs accordingly.<sup>77</sup>

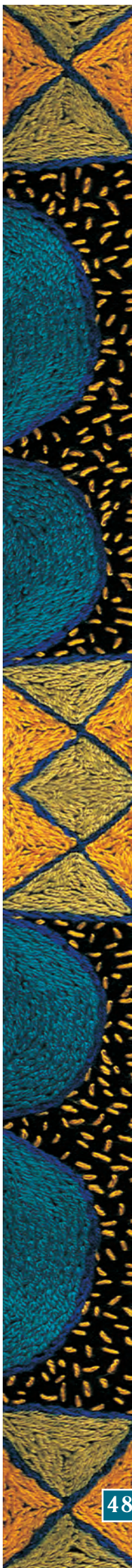
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# MEMBERSHIP



# APPLICATION FORM



**MEMBER FEES FOR 2003**  
*SA HIV Clinicians Society: Private Sector – R250 per annum and Public Sector – R125 per annum.  
These fees are now due.*

**NB PLEASE PRINT LEGIBLY AND RETURN TO:**  
**The South African HIV Clinicians Society, Suite 233, PostNet Killarney, Private Bag X2600, Houghton, Johannesburg, 2041**  
**Tel: +27 (0)11 453 5066, Fax: +27 (0)11 453 5059, E-mail: sahivsoc@iafrica.com**

FIRST NAME ..... SECOND NAME ..... LAST NAME .....  
TITLE ..... DEGREE(S) .....  
SPECIALITY .....  
PHYSICAL ADDRESS .....  
.....HPCSA NUMBER .....  
POSTAL ADDRESS .....  
.....  
CITY .....STATE/PROVINCE ..... COUNTRY .....POSTAL CODE.....  
TELEPHONE NO ..... FAX NO .....  
CELL NO .....  
E-MAIL .....

Please enroll me as a member of the SOUTH AFRICAN CLINICIANS SOCIETY  
Please tick preferred Method of Payment  CHEQUE  DIRECT DEPOSIT  ELECTRONIC TRANSFER  
IN FAVOUR OF THE SOUTH AFRICAN HIV CLINICIANS SOCIETY  
Should you wish to deposit or transfer the membership fee, the Society banks with Nedbank; Branch: Campus Square; Branch code: 158105;  
Account number 1581 048033.  
SIGNATURE ..... DATE .....  
Do you practice in Southern Africa?  YES  NO  OTHER .....RURAL/CITY  
Place of practice? .....  
For how many years have you been treating HIV patients? .....  
Is your area of HIV practice in:  PRIVATE SECTOR  PUBLIC SECTOR  
Do you have any formal training in HIV Medicine?  YES  NO If 'Yes' please specify, .....  
Approximately how many of your patients are currently receiving antiretroviral therapy? .....  
Would you like to become a member of the HIV Clinicians Provider Network?  YES  NO

## MEMBERSHIP BENEFITS

- Quarterly issues *Southern African Journal of HIV Medicine*
- CPD accreditors of Society activities
- Discounted attendance at sponsored conferences
- Regional and international Representation
- Quarterly newsletter *Transcript*
- Website
- Advocacy and professional support
- Education and training courses