

PART ONE: BETTY'S BAY

Salie is a well-nourished 30 year old housewife from Betty's Bay. She is epileptic (as a result of a head injury) and has been well-controlled on carbamazepine 1200mg/day in divided doses for several years. Despite occasionally forgetting her medication – usually when she's had too much to drink – she has not had a seizure for the last two years.

Unfortunately on one of the occasions when she'd overindulged a couple of years back, she was raped. She'd not reported it to the police, and it was only by chance that you, as her healthworker, found out about it. A year ago she had had an episode of shingles, and at her most recent visit for a repeat of her carbamazepine, she mentioned some 'swellings' under her arms and in her groins that she'd first noticed at least six months before. On examining her you discover that she has a generalised lymphadenopathy. After appropriate pretest-counselling, she agrees to an HIV test. The result is positive.

Question 1:

What are the criteria for persistent generalised lymphadenopathy (PGL)?

Answer 1:

- Generalized lymphadenopathy involving two or more extralingual sites lasting 3 months or more
- Absence of an intercurrent disease or illness causing the lymphadenopathy
- Reactive pattern on tissue biopsy (if a biopsy is done)¹

Question 2:

What clinical stage of HIV, according to the WHO staging system, is Salie's infection?

Answer 2:

She is asymptomatic and has PGL – which would fit the criteria for clinical stage 1. However, because she had had a *Herpes zoster* (shingles) infection the previous year, she fits the criteria for clinical stage 2. (See Table 1: WHO staging system for HIV infection and disease.)

Question 3:

What other staging systems or classifications of HIV infection or disease have been developed?

Answer 3:

The Walter Reed Staging Classification (WRSC) has stages based upon i) appearance of lymphadenopathy, ii) progressive depletion of CD4 lymphocytes, iii) appearance of skin test anergy, and iv) presence of oral thrush.⁶

An immunologic staging system (ISS) defines stages with the sequential appearance of: i) CD4:CD8 ratio less than 1.0, ii) absolute CD4 lymphocyte count less than 500/microliter, and iii) total lymphocyte count less than 1500/microliter.⁶ NB: absolute CD4 lymphocyte count = total white blood count x percent lymphocytes x percent CD4 cells.⁷ The ISS does not seem to be used much in clinical settings.

A simplified system has three stages: i) asymptomatic, ii) CD4 lymphocytes less than 400/microliter or oral disease (thrush

Table 1: WHO Staging System for HIV infection and disease²

CLINICAL STAGE 1 – asymptomatic

- Asymptomatic
- Persistent generalized lymphadenopathy (PGL)

Performance scale 1: asymptomatic, normal activity

CLINICAL STAGE 2 – early mild disease

- Weight loss <10% of body weight
- Minor mucocutaneous manifestations (seborrheic dermatitis, prurigo*, fungal nail infections, recurrent oral ulcerations, angular cheilitis)
- Varicella (herpes) zoster virus infection *within the last 5 years*
- Recurrent upper respiratory infections (i.e., bacterial sinusitis)

And/or Performance scale 2: symptomatic, normal activity

CLINICAL STAGE 3 - intermediate (moderate) disease

- Weight loss >10% of body weight
- Unexplained chronic diarrhoea, >1 month
- Unexplained prolonged fever (intermittent or constant), >1 month
- Oral candidiasis (thrush)
- Oral hairy leukoplakia
- Pulmonary tuberculosis *within the past year*
- Severe bacterial infections (i.e., pneumonia, pyomyositis**)

And/or Performance scale 3: bed-ridden, <50% of the day during the last month

CLINICAL STAGE 4 - late (severe) disease (basically equivalent to AIDS)

- HIV wasting syndrome, as defined by CDC³: weight loss of > 10% body weight, plus either unexplained chronic diarrhoea (>1 month), or chronic weakness and unexplained prolonged fever (>1 month)
- *Pneumocystis carinii* pneumonia (PCP)
- Toxoplasmosis of brain
- *Cryptosporidium* with diarrhoea, >1 month
- Cryptococcosis, extrapulmonary
- Cytomegalovirus (CMV) disease of an organ other than liver, spleen, or lymph nodes
- Herpes simplex virus (HSV) infection, mucocutaneous >1 month, or visceral any duration
- Progressive multifocal leukoencephalopathy (PML)
- Any disseminated endemic mycosis (i.e., histoplasmosis, coccidioidomycosis)
- Candidiasis of the oesophagus, trachea, bronchus, or lungs
- Atypical mycobacteriosis, disseminated
- Non-typhoidal *Salmonella* septicaemia
- Extrapulmonary tuberculosis
- Lymphoma
- Kaposi's sarcoma (KS)
- HIV encephalopathy, as defined by CDC³: Cognitive or motor dysfunction interfering with usual activity, progressive over weeks or months in the absence of another condition to explain the findings. Should have brain scan and/or CSF examination to exclude other causes.

And/or Performance scale 4: bed-ridden, >50% of the day during the last month

(Note: both definitive and presumptive diagnoses are acceptable for staging)

* Prurigo nodularis: multiple, intensely pruritic, hyperpigmented/purpuric excoriated nodules erupting on extensor surfaces of the limbs.⁴

** Pyomyositis: a purulent infection of skeletal muscle usually caused by *S. aureus*. It is also sometimes known as tropical pyomyositis or pyomyositis tropicans.⁵

or hairy leukoplakia) present, and iii) both CD4+ depletion and oral disease.⁶

The difficult decision now is whether or not to start treating Salie with antiretroviral agents for her HIV infection. In order to assist with this decision a CD4 count is done. It is 400/l.

Question 4:

Based on her CD4 count, should antiretroviral therapy (ART) be initiated for Salie?

Answer 4:

The optimal time to initiate therapy in asymptomatic individuals with >200 CD4+ T cells is not known.⁸ There are risks and benefits to **delaying** treatment until a later stage; and there are risks and benefits associated with **early therapy**. (See Tables 2 and 3.) However there are other vital issues which will have a major impact on the decision to start therapy. The first is that she fully understands the implications of initiating therapy, the likelihood of adverse effects, the importance of adhering to the regimen (concordance!), the life-long nature of ART, the possibility of the development of viral resistance and the failure of treatment, amongst others. The second is your relationship with her, and the extent to which she trusts you. Don't forget to take her epilepsy and carbamazepine into account as well as her occasional alcohol binges.

Table 2: Risks and benefits of delayed therapy⁹	
Benefits of delayed therapy	
<ul style="list-style-type: none"> • Avoid negative effects on quality of life (i.e., inconvenience) • Avoid drug-related adverse events • Delay in development of drug resistance • Preserve maximum number of available and future drug options when HIV disease risk is highest 	
Risks of delayed therapy	
<ul style="list-style-type: none"> • Possible risk of irreversible immune system depletion • Possible greater difficulty in suppressing viral replication • Possible increased risk of HIV transmission 	

Table 3: Risks and benefits of early therapy⁹	
Benefits of early therapy	
<ul style="list-style-type: none"> • Control of viral replication easier to achieve and maintain • Delay or prevention of immune system compromise • Lower risk of resistance with complete viral suppression • Possible decreased risk of HIV transmission 	
Risks of early therapy	
<ul style="list-style-type: none"> • Drug-related reduction in quality of life • Greater cumulative drug-related adverse events • Earlier development of drug resistance, if viral suppression is suboptimal 	
Limitation of future antiretroviral treatment options	

Question 5

How does 'viral load' influence the decision to initiate therapy?

Answer 5

This is an expensive investigation, and may not be available in some settings. Viral load is particularly helpful in monitoring the efficacy of ART in reducing the numbers of plasma viral

particles, or maintaining as low a level of plasma viral particles as possible. It is therefore very useful to have a baseline measurement if this is possible. Alternatively, one has to rely on the patient's clinical picture, using an instrument such as the WHO staging system referred to above. Table 4 provides guidelines on plasma HIV RNA testing.

Four methods of determining the levels of HIV RNA in plasma or peripheral blood mononuclear cells are presently in use. These are: i) reverse transcriptase-polymerase chain reaction (RT-PCR), ii) branched DNA (bDNA) testing, iii) nucleic acid sequence-based amplification (NASBA), and iv) Lcx luminescence.¹⁰

The reason for being aware of this, is that there is some variation between the different methods and the same method should always be used in monitoring a particular patient's progress. Ideally the specimens would also always be sent to the same laboratory.

Table 4: Indications for Plasma HIV RNA Testing¹¹		
Clinical Indication	Information	Use
Syndrome consistent with acute HIV infection	Establishes diagnosis when HIV antibody test is negative or indeterminate	Diagnosis
Initial evaluation of newly diagnosed HIV infection	Baseline viral load "set point"	Decision to start or defer therapy
Every 3-4 months in patients not on therapy	Changes in viral load	Decision to start therapy
2-8 weeks after initiation of antiretroviral therapy	Initial assessment of drug efficacy	Decision to continue or change therapy
3-4 months after start of therapy	Maximal effect of therapy	Decision to continue or change therapy
Every 3-4 months in patients on therapy	Durability of antiretroviral effect	Decision to continue or change therapy
Clinical event or significant decline in CD4+ T cells	Association with changing or stable viral load	Decision to continue, initiate, or change therapy

It is also possible to have HIV cultures done. However there are several drawbacks – including cost, prolonged time for results to be reported (up to a month), considerable laboratory expertise in performing culture, considerable biohazard to those performing this assay with need for stringent precautions to prevent accidental exposure of laboratory workers, and the possibility of not detecting early infections. Assay of viral reverse transcriptase and use of electron microscopy are additional tools used to assess the growth or cytopathic effects of HIV in cell culture.¹²

Salie's viral load is 60000 copies/ml.

Question 6

Would you start Salie on ART?

Answer 6

With a CD4 count of 400/l and viral load of 60000/ml, Salie falls into a grey area where it is difficult to make hard and fast rules. Many experts believe that the weight of the evidence supports a general guideline that consideration be given to initiating therapy in asymptomatic HIV-infected individuals with a CD4+ T cell count <350/l or a viral load >55,000/ml. For asymptomatic patients with CD4+ T cell counts >350/l, rationale exists for both conservative and aggressive approaches to therapy.¹³

Conservative vs aggressive approaches to initiating treatment in an asymptomatic person.¹³

The conservative approach is based on the recognition that robust immune reconstitution still occurs in most patients who initiate therapy with CD4+ T cell counts in the 200–350 cells/l range, and that toxicities and adherence challenges may outweigh benefits of initiating therapy at CD4+ T cell counts >350 cells/l.

In the conservative approach, higher levels of plasma HIV RNA (i.e., >55,000) are an indication for more frequent monitoring of CD4+ T cell counts and plasma HIV RNA levels, but not necessarily for initiation of therapy.

In the aggressive approach, asymptomatic patients with CD4+ T cell counts >350 cells/l and levels of plasma HIV RNA >55,000 copies/ml would be treated because of the risk of immunologic deterioration and disease progression.

The aggressive approach is supported by the observation that suppression of plasma HIV RNA by antiretroviral therapy is easier to achieve and maintain at higher CD4+ T cell counts and lower levels of plasma viral load. Long-term clinical outcomes data, however, are not available to fully endorse this approach.

In summary, the decision to begin therapy in the asymptomatic patient with >200 CD4+ T cells/l is complex and must be made in the setting of careful patient counselling and education.

After discussing the pros and cons of starting therapy at this stage with Salie, together you decide to repeat her CD4 count and viral load after three months and reassess whether or not to initiate treatment.

Three months later her CD4 count has dropped to 350/l and the viral load has remained more or less the same at 62000 copies/ml. You both agree that it is time to start ART.

Question 7:

What other tests would be useful at this stage in terms of baseline reference values – before she starts her ART?

Answer 7:

- Full blood count
- Liver function tests
- Blood glucose
- Urea and creatinine
- Amylase
- β -HCG

Question 8:

What combination of antiretrovirals are you going to prescribe?

Answer 8:

Highly Active Antiretroviral Therapy (HAART), also known as triple therapy, are combinations of antiretroviral drugs. The usual combinations include nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), and protease inhibitors (PIs).

Standard HAART Regimens¹⁴

- NRTI + NRTI + PI
- NRTI + NRTI + NNRTI
- NRTI + NRTI + PI + PI

One recommended starting regimen is:

- zidovudine and lamivudine – both NRTIs and
- efavirenz – an NNRTI.¹⁵

However, efavirenz produces CNS symptoms (which may include dizziness, somnolence, insomnia, abnormal dreams, confusion, abnormal thinking, impaired concentration, amnesia, agitation, depersonalization, hallucinations, and euphoria¹⁶), and is also teratogenic.¹⁷ As Salie is epileptic it may be wiser therefore not to use this particular NNRTI. It is a mixed inducer/inhibitor of the P450 isoenzyme CYP3A4; and as carbamazepine also probably induces CYP3A4,¹⁶ there is also a chance of a drug interaction. If efavirenz is chosen, then carbamazepine levels should be monitored,¹⁶ and adequate contraception (intramuscular progestogens and a barrier method) should be used.¹⁷

The alternative NNRTI presently available would be nevirapine. However nevirapine's hepatotoxic characteristics, and rapid induction of viral resistance could also make it an unwise choice. Furthermore it too is a CYP3A4 inducer¹⁶ and thus likely to interact with Salie's carbamazepine.

Another possibility would be to substitute the efavirenz with a protease inhibitor. A lipid profile should then be included in the baseline investigations. However, the protease inhibitors inhibit the CYP3A4 isoenzyme¹⁸ and a drug interaction with carbamazepine is possible. If a protease inhibitor is chosen, the recommendation (except for indinavir – for which there was no recommendation¹⁹), is to monitor the carbamazepine levels.²⁰

PART TWO: BARCELONA

The 14th International Aids Conference Barcelona: 7-12 July 2002.

Dr Moodley has highlighted some of the advances made in HIV management. The following paragraphs represent a few vignettes from the conference.

New Thinking in HIV Therapy

Advances in treatment regimens include:

- once daily treatment regimens
- structured treatment interruptions(STI),
- protease inhibitor(PI) and nucleotide reverse transcriptase inhibitor(NRTI) sparing regimes,
- a new fusion inhibitor (FI) – T20, and
- integrase inhibition(II)

Once daily treatment regimens

2 studies were presented: Baril et al²¹ in Canada, and Peytavin et al²² in France, underscored the importance of simpler regimens in improving drug adherence, especially in patients with previous failure of antiretroviral therapy (ART). In both these studies a once daily saquinavir/ritonavir combination was tested. Other once daily formulations include efavirenz, enteric coated didanosine, and tenofovir. A novel once daily PI – atazanavir – is currently in phase 3 development.

Structured Treatment Interruptions(STI)

STI in patients who have already responded to HAART, represent a potential means of preserving drug sensitivity and enhancing the quality of life of HIV infected patients.

2 studies were presented: Gallant²³ found in his study of 75 patients that 69% of the cohort remained off treatment after a mean treatment interruption (TI) of 69 weeks. He concluded that the best candidates for STI are those with higher baseline CD4 counts and lower viral loads – those patients who are less likely to be treated based on current guidelines if a conservative approach is adopted. However, safety and durability of prolonged TI need to be assessed further.

Garcia²⁴ found that 41% of his 44 patients achieved a response to STI. His conclusion was that a preserved memory response in CD4+ cells may be the most important determinant of a favourable response to STI.

PI- and NRTI-sparing HAART regimens

The preservation of future treatment options for as long as possible, by 'sparing' the use of a class-sparing regimen is another tool being studied to maximize the benefits of antiretroviral therapy. The goal of a class-sparing regimen is to preserve or "spare" one, or more than one, class of drugs for later use. Moreover, this strategy makes it possible to selectively delay the risk of certain side effects uniquely associated with a single class of drugs.²⁵

Raffi²⁶ presented preliminary data from an NRTI-sparing study in 100 patients using a lopinavir-ritonavir combination plus efavirenz. Week 16 data indicate favourable antiretroviral potency and immunologic activity. The study will be continued for 48 weeks.

Table 5: Advantages and Disadvantages of Class-Sparing Regimens²⁷

Regimen	Possible Advantages	Possible Disadvantages	Drug Interaction Complications	Impact on Future Options
PI-based HAART regimen (NNRTI sparing)	<ul style="list-style-type: none"> Clinical, virologic, and immunologic efficacy well-documented Continued benefits sometimes seen despite viral breakthrough Resistance requires multiple mutations Targets HIV at two steps of viral replication (RT and PI) 	<ul style="list-style-type: none"> May be difficult to use and adhere to Long-term side effects may include lipodystrophy, hyperlipidaemia, and insulin resistance 	<ul style="list-style-type: none"> Mild to severe inhibition of cytochrome P450 pathway; ritonavir is most potent inhibitor, but this effect can be exploited to boost levels of other PIs 	<ul style="list-style-type: none"> Preserves NNRTIs for use in treatment failure Resistance primes for cross-resistance with other PIs
NNRTI-based HAART Regimen (PI-sparing)	<ul style="list-style-type: none"> Sparing of PI-related side effects Generally easier to use and adhere to compared with PIs 	<ul style="list-style-type: none"> Comparability to PI-containing regimens with regard to clinical endpoints unknown Resistance conferred by a single or few mutations 	<ul style="list-style-type: none"> Fewer drug-drug interactions compared with PIs 	<ul style="list-style-type: none"> Preserves PIs for later use Resistance usually leads to cross-resistance across entire NNRTI class
Triple NRTI Regimen (NNRTI- and PI-sparing)	<ul style="list-style-type: none"> Generally easier to use and adhere to compared with PIs Sparing of PI and NNRTI side effects Resistance to one NRTI does not confer cross-resistance to entire class 	<ul style="list-style-type: none"> Comparability to PI-containing regimens with regard to clinical endpoints unknown Long-term virologic efficacy with high baseline plasma viral load (i.e., >100,000 copies/ml) may be suboptimal 	<ul style="list-style-type: none"> Generally manageable drug interaction problems 	<ul style="list-style-type: none"> Preserves both PI and NNRTI classes for later use Limited cross-resistance within the NRTI class

T20

T20 is an investigational fusion inhibitor – enfuvirtide. It is a synthetic inhibitor of gp41-mediated fusion. T20 is administered twice daily by subcutaneous injection. The findings of 2 large scale phase 3 studies were released at the conference – TORO 1 (Americas) – involving 491 study participants, and TORO 2 (Europe and Asia) – involving 504 participants. Study results thus far indicate that the addition of T20 to optimized conventional treatment is associated with significant and prolonged viral suppression in heavily pre-treated patients. It

is ideally suited for patients who develop resistance to existing treatment. However, at \$10000–\$12000 per patient per year, it is the most expensive antiretroviral to date, and hence highly inaccessible in resource depleted settings.

Integrase Inhibitors

Integrase is one of 3 enzymes required for HIV to replicate in the body. Reverse transcriptase and protease have already been used in developing treatments for HIV. Integrase inhibitors stop HIV from inserting its genes into normal DNA. This drug, presently being developed, might be on the market in 4 years.

Conclusion

These advances in HIV treatment are however of little relevance to resource depleted countries facing the greatest HIV/AIDS burden of disease. Some parts of Africa have to make do with "hand me down" antiretrovirals from the United States. These "second-hand" drugs have been provided to about 50 Nigerians by the US based Starfish Project, an organization that collects unused prescription medication of American AIDS patients from New York to Hawaii. The drugs are from patients who have either changed or abandoned their own medical regimens. The drugs are screened by medical staff linked to the project at Cornell University prior to distribution in Nigeria.

For developing countries, it is an HIV vaccine rather than a wider selection of antiretrovirals that is urgently needed. Two impressive presentations on the world's first HIV vaccine trials currently in progress were made.

1. Harro et al²⁸ reported on their study: 'Conduct of the first phase 3 efficacy trial of a preventive HIV 1 vaccine (AIDSVAX B/B) in North America and Europe'. This randomized double blind placebo controlled (2:1) trial is intended to evaluate the efficacy of a bivalent clade B HIV vaccine in preventing HIV infection in North America and Europe. Subjects were vaccinated at months 0,1,6,12,18,24 and 30. The study was powered to detect a vaccine efficacy of 30% (lower limit). Subjects were enrolled from June 1998 to October 1999. Participants included 5109 men who have sex with men (MSM) and 309 women at heterosexual risk. The sample is generally young (median age 36 years), white (83%) and well educated (61% have a college education or higher). Two years after enrollment, there was 89% retention of study participants. Risk behaviour did not increase. There were no vaccine-related serious adverse events (SAEs). The most common adverse event was pain at the injection site. Three percent of participants experienced social harm as a result of participation in the study. This trial ends later this year.

2. Choopanya et al²⁹ presented the world's first phase 3 efficacy trial of an HIV vaccine in the developing world. This ongoing follow-up study of injecting drug users (IDUs) in the AIDSVAX B/E efficacy trial is taking place in Bangkok, Thailand. HIV negative IDUs have been randomized to receive placebo or AIDSVAX B/E in a 1:1 ratio at months 0,1 and 6 with boosters at months 12,18,24 and 30. The primary endpoint is HIV infection with the secondary endpoint being an altered course of disease as evidenced by CD4 counts and viral load. A follow-up of 3 years is planned. This study is also powered to detect a vaccine efficacy of at least 30%. 2545 volunteers have been enrolled. The median age of the sample is 26 years and 93% are male. Immunisation compliance is 98%. Follow-up so far has been excellent and like the North American Study, there have been no vaccine related SAEs or adverse events except for injection site pain and tenderness. At 6 months, risk behaviour has decreased and condom use has increased. Final results are expected late next year.

At this point in the HIV pandemic, a preventive HIV vaccine remains the most promising intervention which may effect a change in the course and magnitude of the pandemic. Much hope has been attached to the vaccine and it is believed that even a partially effective vaccine will lead to a tangible difference. The challenges however, rest with the logistics of registering a partially effective vaccine with regulatory authorities, and the knowledge that participants in early vaccine trials will be excluded from participating in later trials of more efficacious vaccines.

In South Africa, it has been established that the clade C virus is predominant and as such, most studies of the vaccine here should, for ethical reasons, be based on a clade C vaccine. Such vaccines will only be ready for trials in 3-5 years. Hope is also resting on the possibility that cross-clade reactivity may be induced, which might make it possible to test different vaccine clades in different parts of the world. This possibility of cross clade reactivity also raises the potential for a trivalent vaccine

that could be used universally to cover the most common viral subtypes globally.

Apart from the scientific, safety, and statistical challenges posed by HIV vaccine trials, a myriad ethical issues have been raised, especially where such research is conducted in developing countries. These issues include adequately obtaining informed consent from educationally disadvantaged participants; providing antiretroviral treatment to participants who become HIV positive during the course of the study; and the availability of the vaccine in the developing world, if it is shown to be effective in a study. What has become abundantly clear is that it will be unethical to conduct HIV vaccine trial in developing sites anywhere in the world without intense community-preparation-programs being implemented.

Ultimately, Barcelona succeeded in hosting a stimulating and vibrant conference and the HIV community eagerly awaits the 15th international conference in Thailand in 2004.

References

1. Klatt EC. Pathology of AIDS version 11. Florida State University College of Medicine. 2002:58
<http://medstat.med.utah.edu/WebPath/AIDS2002.PDF> (accessed 02/11/2002)
2. *ibid*:60
3. Dybul M, Fauci AS, Bartlett JG, Kaplan JE, Pau AK. Guidelines for Using Antiretroviral Agents Among HIV-Infected Adults and Adolescents. *MMWR* 2002;51 (RR07).
<http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5107a1.htm> (accessed 02/11/2002)
4. Mason SH, Hogan D. Prurigo nodularis. www.emedicine.com/DERM/topic350.htm (accessed 02/11/2002)
5. Al-Tawfiq JA, Sarosi GA, Cushing HE. Pyomyositis in the Acquired Immune Deficiency Syndrome. *Southern Medical Journal*. 2000;93(3):330-4.
<http://www.sma.org/smj2000/marsmj00/altawfiq.pdf> (accessed 03/11/2002)
6. Klatt p61
7. Roytowski D. Current Review of HIV in South Africa.
<http://www.wits.ac.za/fac/med/ophthalmology/opjun01.htm> (accessed 02/11/2002)
8. Panel on Clinical Practices for Treatment of HIV Infection. Guidelines for Using Antiretroviral Agents Among HIV-Infected Adults and Adolescents. Department of Health and Human Services (DHHS) and the Henry J. Kaiser Family Foundation. 2002:37
http://www.hivatis.org/guidelines/adult/May23_02/AAMay23.pdf (accessed 02/11/2002)
9. *ibid*:35
10. Klatt. *op cit*:42
11. Panel on Clinical Practices. *op cit*:33
12. Klatt. *op cit*:43
13. Panel on Clinical Practices. *op cit*:8-9
14. Klatt. *op cit*:32
15. The Southern African HIV Clinicians Society. Guidelines on Antiretroviral Therapy In Adults. 2002:7 (available from: sahivsoc@iafrica.com)
16. Panel on Clinical Practices. *op cit*:46
17. SA HIV Clinicians Society. *op cit*:4
18. Panel on Clinical Practices. *op cit*:47,48
19. *Ibid*:53
20. *Ibid*:53,54
21. Baril et al
22. Peytavin et al
23. Gallant
24. Garcia
25. Panel on Clinical Practices. *op cit*:14
26. Raffi
27. Panel on Clinical Practices. *op cit*:42
28. Harro et al
Choopanya et al

LEARN
QUESTION
DEBATE
SHARE



S.A.
Family Practice
The only On You NEED to Read!

Be Proactive, be Professional, get Involved with your Future!
Join the South African Academy of Family Practice/ Primary Care
CALL PENNY BRYCE ON 011-807 6605