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Module 4

Safe and Effective Use of Antiretrovirals

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Module 4
Safe and Effective Use of Antiretroviral Treatment

This module provides guidance primarily to clinicians, both doctors and nurses, counsellors, and managers of clinical services. Policy makers, people living with HIV/AIDS (PLHA), and mid-level decision makers in major and district hospitals, and in training institutions, may also find this guidance useful.

1. Introduction

In recent years powerful antiretroviral (ARV) treatment regimens have become available. So far, with a few exceptions, only people living with HIV/AIDS from industrialised countries have benefited from these treatments. In a proportion of patients, triple combination ARV therapies reduce viral load plasma levels to undetectable levels and have a beneficial clinical effect. HIV-related symptoms may disappear, the incidence of opportunistic infections is reduced and quality of life improves. Triple therapy has decreased dramatically the number of hospitalisations for HIV-related illness in industrialised, and some middle income, countries and prolonged the lives of many people with HIV.

However, these treatments are not a cure for AIDS and their long term effectiveness is not yet known. Resistance may develop even in patients who adhere strictly to the regimen. Combination therapy including protease inhibitors is most effective in patients who have never been treated with ARVs. In patients who have already taken ARVs however, up to 40% treatment failure has been observed after one year of treatment. HIV may persist in "sanctuary sites" where the drugs cannot suppress viral replication. Studies have shown that after 20-30 months of successful combination ARV treatment, HIV can still be isolated despite patients having undetectable HIV RNA plasma levels. This suggests that ARV treatment cannot be stopped; it is a treatment for "life" unless or until it fails, or until current regimes are superseded by new drug combinations.

Current ARV therapy is far from ideal. The regimens are complicated, requiring between 2 and 20 pills a day, they may cause severe side effects, they require close and often expensive laboratory monitoring, and there may be interactions with other drugs. Finally, the drugs themselves are very costly. In May 1998, the annual cost of triple therapy including a protease inhibitor amounts to US$ 10,000 - 15,000. ARV treatment guidelines change rapidly and differ between countries. It is expected that more powerful drugs and easier regimens will become available in the near future.

Currently available ARVs belong to two major classes of drugs: reverse transcriptase inhibitors (RTIs) and Protease Inhibitors (PIs). RTIs are further divided into Nucleoside Reverse Transcriptase Inhibitors (NRTI) and Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTI).

All these drugs target enzymes which are important for RNA replication and viral functioning. Once the HIV retrovirus has invaded a macrophage or T-lymphocyte, the enzyme HIV reverse transcriptase converts the viral RNA genome into a DNA copy, which is then integrated into the host chromosome by the enzyme integrase. A third enzyme, protease, contributes to viral functioning by catalysing the cleavage of viral core proteins for the final assembly of viable virions. Once HIV is integrated into the host DNA, the virus multiplies rapidly, creating several billion new copies a day. This inevitably results in mutations of the viral genome. Some of the mutations may confer resistance to one specific agent or to a whole class of ARVs.

In most industrialised countries eleven antiretroviral agents have been approved for treatment. Other classes of drugs are under development. (See section on specific drugs including Tables 9-14 for detailed information on each of the drugs.)

Good adherence to the ARV regimen is essential to avoid development of resistant strains. However, the regimens are complicated and adherence is difficult even in the most favourable circumstances; a very supportive environment, materially and socially, is required.

Combination therapy requires taking drugs twice or three times a day at regular time intervals. There are often adverse effects, and the drugs have to be taken for life. One of the protease inhibitors (Ritonavir) requires refrigeration and other ARVs must be taken with large quantities of water (see drug data sheets at end of the document). Patients may also have to take other drugs to prevent or to treat opportunistic infections. Adherence to such a complicated treatment for a person who has little knowledge about the disease, has many other problems, eats only when food is available and has no watch, is not an easy task. A physician who has only a few minutes per patient cannot adequately explain the regimen and support the patient's adherence. Moreover, because of the stigma associated with HIV infection, individuals may be reluctant to reveal their seropositivity to others. Therefore, except for the health care staff, no one will be able to help them to adhere to their ARV regimen.

Many clinicians do not have enough time to provide adequate counselling about HIV. If counsellors are available, they will need special training in ARVs and will work closely with the prescribing clinician. In many settings clinicians do not have enough time per consultation to explore all the client's concerns and questions about ARVs and adherence. The client may in any case feel uncomfortable discussing "non-medical" issues with his or her doctor and may prefer talking to a counsellor. The physician will have to make extra time to counsel patients on ARV treatments, and he/she may need extra training to improve counselling skills or may choose to work closely with a counsellor.

2. What needs to be in place before initiating ARV therapy

Due to their high cost , the complexity of regimens and need for careful monitoring, certain services and facilities must be in place before considering the use of ARVs in any situation.

Conditions necessary to introduce ARVs

- Access to functioning and affordable health services and support networks into which ARV treatments can be integrated so that the treatments are provided effectively.
- Information and training on safe and effective use of ARVs for health professionals in a position to prescribe ARVs.
- Capacity to diagnose HIV infection and to diagnose and treat concomitant illnesses.
- Assurance of an adequate supply of quality drugs[1].
- Sufficient resources should be identified to pay for treatment on a long term basis; patients must be aware that treatment is "for life".
- Functioning laboratory services for monitoring including routine haematological and biochemical tests to detect toxicities, must be available[2].
- Access to voluntary HIV counselling and testing (VCT) and follow up counselling services should be assured, including counselling PLHA on the necessity of adherence to treatment.

[1] See Module 8 on drug regulatory mechanisms and safeguards for storage, distribution and prescription for further details.
[2] See Module 5 laboratory requirements for safe and effective use of ARVs for further details.

Advantages and disadvantages of ARV treatment

There are advantages and disadvantages to using ARVs at *any stage* of HIV disease and it is important for the physician and patient to consider these before embarking on difficult and costly treatment.

Advantages

- A longer life.
- Disappearance of symptoms, improved quality of life in symptomatic patients, delayed disease progression, fewer opportunistic infections.
- Decreased risk of hopitalization.
- Control of viral replication.

Disadvantages

- Impairment of the quality of life in particular for the asymptomatic patient because of the difficult treatment regimen or adverse reactions.
- Development of drug resistance and cross resistance when patients are treated with a sub optimal (bi- or mono-) ARV treatment regimen, when viral load monitoring is not possible (to detect treatment failure) or when patients do not adhere to ARVs. Such resistance will limit the treatment options in the future and increase the risk of transmission of resistant strains.
- Raising false hopes in a proportion of patients who will either not respond or not tolerate the therapies.
- Potential toxicity during pregnancy.
- The cost. Money spent on ARVs is then not available for other essential items for the family, which may also improve the quality of life of the person living with HIV infection.

3. When to initiate antiretroviral therapy

As yet it is not clear when is the best time to start combination therapy. The recommendations for ARV treatment in industrialised countries are often based on virological criteria, but not on clinical outcome or quality of life data (proven clinical efficacy).

Table 1 Suggested priority to be accorded to ARV treatment according to disease stage and available laboratory facilities

Disease stage (WHO stage 1-4)	Tests available		
	No CD4 counts No viral loads	Only CD4 counts	CD4 counts Viral loads
1. Acute HIV illness	No ARVs	No ARVs	No priority
Asymptomatic phase	No ARVs	Limited priority	Limited priority
2. Early symptomatic phase	No ARVs	Limited priority*	Limited priority*
3. Symptomatic phase, non-AIDS	Limited priority**	ARVs***	ARVs***
4. AIDS	ARVs***	ARVs***	ARVs***
5. Terminal AIDS	No ARVs	No ARVs	No ARVs

* Depending on available resources, CD4 count and/or viral load results, bitherapy, or ideally tritherapy, could be considered.

** Depending on available resources bitherapy, or ideally tritherapy could be considered.

*** Start ARV treatment based on CD4 count and/or viral load results. With only a small budget it is probably best not to start too early with ARV treatment to allow the continuation of this treatment once it has been started. A maximum benefit on the quality of life of patients is expected in patients with CD4 counts < 200/mm^3 and/or a viral load > 30.000-100.000 copies/ml plasma.

3.1 Acute HIV illness

In industrialised countries ARV treatment is sometimes recommended in the acute phase of the illness. The data currently available however suggest that even with early, highly active antiretroviral therapy (HAART), eradication of HIV is not possible. Starting ARV treatment during the acute phase of the illness is very expensive as it must continue for life. Moreover, an acute HIV illness is generally not recognised in many developing countries because such episodes are difficult to distinguish clinically from other infections prevalent in these parts of the world, such as malaria or typhoid fever.

When resources are limited, there is therefore a strong case against using ARVs for this indication.

3.2 Asymptomatic patients

In most industrialised countries ARV treatment is recommended in asymptomatic patients with plasma HIV RNA levels greater than 5,000 to 10,000 copies per ml regardless of the CD4 cell count. However, even in industrialised countries, many asymptomatic patients choose *not to* take ARVs, because although there may be theoretical reasons to take ARVs, the complex and unpleasant regimes may outweigh the benefits at this stage. Furthermore many people are deciding to wait rather and remain "ARV naive" so that when more powerful, simpler and less costly drugs become available they can still benefit. ARVs often cause side effects, the regimens are complex and the long term benefits have not been demonstrated for this specific group of patients.

Disadvantages of "early combination ARV treatment" in asymptomatic HIV disease

1. In asymptomatic patients, ARVs may decrease the quality of life because side effects are common and taking large numbers of pills at regular time intervals may interfere with employment and daily activities and can be very stressful.
2. Long-term ARV treatment is very expensive.
3. Resistance may develop, reducing treatment options in the future. Long-term, strict adherence to ARV treatment may be difficult to maintain (leading to resistance).
4. Asymptomatic patients may be less willing to adhere to difficult ARVs regimens than symptomatic patients, because ARVs do not obviously improve their lives and have significant side effects.
5. Adverse consequences of some ARVs such as lacticacidosis and pancreatitis may be life threatening.
6. The long term side effects of ARV drugs remain unknown.

Treatment of asymptomatic people in resource poor countries is problematic. Firstly, it has to be determined whether an asymptomatic patient really is HIV infected. The HIV test result should therefore be reliable and accompanied by adequate counselling. Recently the World Health Organisation and UNAIDS have developed new guidelines for HIV testing *(Revised recommendations for the selection and use of HIV antibody tests, 1997).* A positive HIV test (rapid or ELISA) should be confirmed by at least one other test (also rapid or ELISA). Resources should be available to implement these guidelines.

Secondly, to decide when to start ARV treatment in an asymptomatic patient, it is recommended that a reliable CD4 lymphocyte count and viral load test be performed. Both tests require a sophisticated laboratory and trained personnel. At the time of writing a viral load test costs about US$ 100 per

test. Some commercially available viral load tests perform less well with certain HIV genotypes that are frequently seen in poor countries, though the most recent tests have largely overcome this problem.

Thirdly, in many countries the stigma associated with HIV remains high. Women are often unable to tell their partner that they are HIV seropositive because they risk being abandoned. A person may lose his/her job when it is known that he/she is HIV seropositive. People may be reluctant to accept ARV treatment because having to take so many pills is difficult to hide and may reveal their seropositivity to others. Furthermore, in poor countries with limited ARV availability, access to ARVs may be limited to symptomatic patients, as the priority group. (See Modules 2 and 3 for further details)

Thus in countries where resources for ARV treatments are limited, it may be difficult to argue for treatment for asymptomatic individuals.

3.3 Symptomatic patients

ARVs are certainly beneficial for symptomatic patients. Opportunistic infections occur less often and patients may even become completely asymptomatic for a substantial period of time. Current recommendations are however, to continue with prophylaxis against certain OIs, (such as cotrimoxazole for *pneumocystis carinii* pneumonia in industrialised countries and for pulmonary infections and septicaemia in developing countries, and isoniazid prophylaxis for TB in HIV-infected people at high risk of developing TB, especially in developing countries) even if CD4 count rises. There are many case reports of patients with CMV, cryptosporidiosis, wasting or chronic diarrhoea whose symptoms have resolved after starting triple therapy.

Disadvantages of ARVs in symptomatic patients in poor resource settings.

1. There are particular problems in prescribing ARVs to patients who are taking certain anti-tuberculosis drugs (see section on TB and ARVs). However, there is no contraindication to taking ARVs with standard isoniazid TB preventive therapy.
2. Symptomatic patients may have more difficulty tolerating ARVs than asymptomatic patients because they already have symptomas such as nausea because of gastro-enteritis. Adverse events may also occur more often in symptomatic patients because of pre-existing liver disease, polyneuritis or renal insufficiency.
3. ARVs interact with certain drugs used to treat opportunistic infections.

Despite these possible disadvantages, treatment of symptomatic patients is the norm in industrialised countries. In developing countries where resources are available for ARV treatment, treatment of symptomatic patients should take priority over treatment of asymptomatic patients.

3.4 Terminal HIV and palliative care

Patients with terminal HIV disease, such as widespread malignancy and patients who are severely immunocompromised (CD4 <10) will rarely respond to ARV therapy and initiating therapy at this stage may be a waste of limited resources and a burden to the patient. As stated earlier, ARV therapy should be provided in the context of a continuum of care for PLHA. If treatment fails or patients have terminal HIV and do not respond to ARV therapy, adequate palliative care and emotional and spiritual support should be provided. Referral to a home based care team, if available, for management of pain and symptomatic relief is important if the patient chooses not to remain hospitalised. It is also important to have bereavement counselling available for carers and family members.

4. ARV treatment in clinical practice: the steps to follow

Table 2 lists the steps that should be followed by the clinician when considering initiating ARV therapy at any stage of HIV disease.

Table 2

ARV treatment in clinical practice

1. **HIV pretest counselling**
2. **Obtaining informed consent**
3. **HIV testing**
4. **HIV post test counselling**
5. **Medical consultation**
   - **medical history**
   - **physical examination, including weight**
   - **STD screening**
   - **TB screening (ideally including a chest Xray)**
   - **routine haematological and biochemical tests**
   - **other tests to diagnose opportunistic infections if indicated**
   - **pregnancy test if indicated**
   - **CD_4 lymphocyte count (highly recommended), viral load (if available)**
6. **Follow-up visit to discuss**
   - **results of medical check-up**
   - **treatment options including the risks and benefits of ARV treatment**
7. **Choose the optimal ARV treatment regimen and explain it in detail.**
8. **Provide the ARVs and organise drug counselling in order to obtain optimal adherence.**
9. **Provide ongoing counselling including advice on safer sex and family planning**
10. **Monitor the ARV treatment : clinically, biologically, and for adherence.**

5. Which antiretroviral regimen to initiate

5.1 Triple combination therapy

The treatment of choice is triple combination therapy including at least one protease inhibitor with potent *in vivo* activity (indinavir, ritonavir, nelfinavir and the new formulation saquinavir). An alternative may be triple combination therapy with ritonavir, saquinavir and an NRTI. Less potent regimens are 2 NRTIs + 1 NNRTI. It is generally recommended that the combination should include a drug that penetrates well into the brain such as zidovudine or stavudine.

Nucleoside analogue combinations that could be used in triple therapy are:

- zidovudine (ZDV) + didanosine (ddI)
- zidovudine (ZDV)+ lamivudine (3TC)
- stavudine (d4T) + lamivudine (3TC)
- stavudine (d4T) + didanosine (ddI)

The above are roughly equivalent. Zidovudine (ZDV) and zalcitabine (ddC) in combination are less active and are regarded as second tier.

Certain combinations are *not* advisable, because of overlapping toxicity:

- didanosine (ddI) + zalcitabine (ddC)
- stavudine (d4T) + zalcitabine(ddC)

or because of an antagonistic effect due to overlapping intracellular phosphorylation pathways:

- zalcitabine(ddC) + lamivudine(3TC)
- stavudine(d4T) + zidovudine (ZDV)

Table 3 Examples of triple therapy regimens including a protease inhibitor

Initial regimen	Alternative combination
ZDV + 3TC + PI_1*	D_4T + DDI + PI_2** Ritonavir + Saquinavir + NRTI
D_4T + 3TC + PI_1	ZDV + DDI + PI_2 Ritonavir + Saquinavir + NRTI
ZDV + DDI + PI_1	D_4T + 3TC + PI_2 Ritonavir + Saquinavir + NRTI
D_4T + DDI + PI_1	ZDV + 3TC + PI_2 Ritonavir + Saquinavir + NRTI

5.2 Double combination therapy

Double combination therapy (2 NRTIs) produces clinical and virological improvement, but is inferior to triple therapy . However, many patients in industrialised countries continue to take bitherapy either because they do not want to take more complicated tritherapy regimes or because they do not want to "use up all their options." Double therapy could also be considered if patients do not tolerate triple combination regimens or if there are contraindications for the use of protease inhibitors. Double therapy can also be used where protease inhibitors are not available or affordable. Double combination therapy with 2 NRTIs is generally well tolerated and is easier to monitor than triple combination therapy.

When double therapy with two nucleoside analogues is failing, adding only a protease inhibitor without changing the NRTIs (because alternative ARVs drugs are not available) may lead to rapid resistance against protease inhibitors since the protease inhibitor then behaves as monotherapy. Double combination of one NRTI and one protease inhibitor has a stronger antiviral effect but also leads to resistance against the protease inhibitor.

6. How to monitor ARV treatment

It is advisable for patients on triple therapy to be seen monthly; particularly at the start of treatment. Once stabilised, patients may then be seen every three months. At each visit, side effects and adherence to the treatment should be discussed in depth. At the start of treatment, routine haematological and biochemical tests should be done monthly to detect potential side effects. Careful monitoring is needed particularly in patients who abuse alcohol or are infected with hepatitis B or C, who have abnormal liver function, and in patients with abnormal renal function. The appearance of

* PI with potent in vivo activity : indinavir, ritonavir, nelfinavir

** The best alternative PI after failure on an initial PI containing regimen is unknown. Cross-resistance between indinavir and ritonavir is almost total.

certain symptoms such as nausea, anorexia or abdominal pain is a reason for repeating certain laboratory tests.

Ideally, *if available*, viral load and /or CD4 count should be measured regularly, e.g., in untreated patients every 6 - 12 months and in patients on ARVs every 3 - 6 months.

The results of viral load testing should be interpreted with caution. Certain viral strains that are particularly frequent in developing countries may be difficult to detect with commercially available testing methods; and viral load levels may vary according to the technique that has been used, the laboratory where the test has been done, the time and the way the sample was transferred to the laboratory. Levels may increase after a recent infection or vaccination. An increasing viral load does not necessarily mean that the ARV treatment is not effective. It may be that the patient is not adhering to the treatment. There may also be problems in measuring CD4 counts in developing country settings (for further details on laboratory monitoring see Module 5).

Treatment decisions should take into account these possible variations and the clinical condition of the patient, information about adherence and availability of ARVs to which he/she could switch. Ideally a viral load measurement should be done before starting and before changing ARV treatment; and 1 to 2 months after the start of the initial or new treatment. Where viral load testing is not available CD4 counts can be used instead to guide initiation and monitoring of ARV treatment. CD4 lymphocyte counts are also used to decide whether the patient should receive prophylactic treatment against opportunistic infections. Ideally, in countries where ARVs are introduced, a reference laboratory should be established where these tests could be performed (see Module 5 for further details).

In developing countries where CD4 counts or viral loads are not routinely available, clinical indicators such as weight and total lymphocyte count will give some indication of disease progression and treatment response.

Table 4 Laboratory monitoring during ARV treatment

	Bitherapy	Tritherapy (including a protease inhibitor)
Haematocrit/haemoglobin	X	X
White blood cell count + differential	X	X
Platelets	X	X
Bilirubin	X	X
Transaminases	X	X
Amylase	X	X
Creatinine/Urea/Urine proteinalysis	X*	X**
Creatinine phosphokinase	X*	X**
Glucose/Glucose urine analysis		X**
Triglycerides		X**
CD_4 lymphocytes count	X**	X**
Viral load		X

* Advisable, but not essential

**Highly recommended, but not essential

7. Changing antiretroviral therapy

7.1 When to change?

Reasons for changing ARV treatment are: treatment failure, toxic effects, intolerance, non-adherence, and current use of a sub-optimal treatment regimen (Table 5). In industrialised countries definitions of treatment failure are based on viral load measurements - a rising plasma viral RNA level or failure to achieve the desired reduction in plasma viral load. A declining CD4 count is also an indication to change treatment (see Module 5 for further details). In settings where it is not possible to do viral load tests and CD4 counts, weight loss and other clinical changes may provide a good indication of the need to change treatment.

Asymptomatic patients currently taking double NRTI combination treatment with undetectable plasma HIV RNA levels should be closely monitored. If plasma HIV RNA levels increase above 5,000 to 10,000 copies per ml, the treatment regimen should be changed. In the absence of laboratory facilities to measure viral load, decisions to change treatments should be based on results of CD4 lymphocyte counts and/or clinical condition, including weight of the patient.

Factors other than viral resistance that can lead to loss of viral suppression are: non-adherence to treatment and intercurrent illnesses. To evaluate the efficacy of an ARV regimen, viral load should not be measured in the days following a vaccination. If during ARV treatment a patient develops side effects, the offending drug should be replaced by another drug with a different toxicity profile. If the cause of the side effects is not clear, a brief and complete interruption of the full therapeutic regimen is generally preferred. Because ARVs may have to be changed it is not ideal to start ARV treatment when only a limited number of ARVs are available - often the case in developing countries. If the ARV drug is stopped because of intolerance or side effects and no alternative treatment is available, resistance may develop rapidly.

Table 5 Indications for changing therapy

1. Treatment failure :

Clinical disease progression

Declining CD4 count

Failure to achieve the desired reduction in viral load :

viral response = reduction of viral load > 2 log HIV RNA copies (100 fold) or viral load levels below detectable levels

Rising plasma viral load

viral load rebound to 0.5 log HIV RNA copies above the level of maximum virological response (nadir)

2. Unacceptable toxicity, intolerance or non-adherence

3. A sub-optimal treatment regimen : e.g. ARV monotherapy

7.2 What to change to?

When treatment failure occurs all drugs in the regimen should be changed if possible, because it is currently impossible to determine which of the combination's drugs is the one to which resistance has developed. Changing both drugs in a double NRTI combination regime or changing a protease inhibitor and a NRTI in a three-drug combination is advised. Simply adding a protease inhibitor or any other drug to a failing regime is never recommended.

Table 6 Predicting the effectiveness of switching therapy

Switching combinations	Likely effectiveness
Switching NRTI combinations	
ZDV+3TC ⟶ d4T+ 3TC	probably not effective
d4T+ddI ⟶ ZDV+3TC	may be effective
ZDV+ddI ⟶ d4T +3TC	may be effective
ZDV+3TC ⟶ d4T+ddI	may be effective
Switching protease inhibitors*	
nelfinavir ⟶ ritonavir/saquinavir	may be effective
ritonavir/saquinavir ⟶ nelfinavir	may be effective
ritonavir/saquinavir ⟶ indinavir	probably not effective
indinavir ⟶ ritonavir/saquinavir	may be effective
indinavir ⟶ nelfinavir	probably not effective
nelfinavir ⟶ indinavir	probably not effective

*** There is a great deal of cross resistance between the protease inhibitors, therefore switching protease inhibitors in cases of treatment failure is rarely successful.**

When changing because of non-adherence, the reasons for non-adherence must be explored. For example, if a patient does not like to take three times daily (tds) regimen, a twice daily (bd) regimen may be proposed. If a change in therapy is needed because of drug toxicity, only the drug causing the toxicity should be replaced.

8. Special considerations

8.1 ARV treatment in women of childbearing age

Before considering ARV treatment in a woman, a pregnancy test may be required. Data on ARVs in pregnancy is limited, particularly in the first trimester. A study in the USA is currently assessing potential foetal risks. So far we know that zidovudine given in the second or third trimester does not cause congenital malformations. The long-term effect of zidovudine on the child's health remains

unknown. As regards the other ARVs, very little is known about their potential toxicity for the foetus (see Module 6 for more details).

Triple therapy, therefore, should probably not be prescribed for women during early pregnancy or for women at risk of pregnancy. Contraception is recommended for all women considering combination ARV treatment. When a woman treated with bi- or triple combination therapy becomes pregnant, the risks of such treatment for the foetus should be discussed. The physician or counsellor should discuss family planning with all women before starting ARVs.

If a woman becomes pregnant whilst taking ARVs the counsellor will have to help her decide whether to continue with the pregnancy or whether to have a termination, if this is available. The desire to have a child for many women is of great importance and may override medical concerns. Once the decision has been made to have a baby or to continue with a pregnancy this decision should be supported by the counsellor and ARV therapy may have to be modified during this period. The possible detrimental effects to the mother of altering her ARV treatment during pregnancy must also be discussed.

8.2 ARV treatment in children with HIV (see Module 6 for further details on ARVs to reduce mother-to-child transmssion).

In infected children in industrialised countries ARV treatment is continued after birth particularly in children with a poor prognosis (high viral load, symptomatic). If a child becomes infected despite zidovudine prophylaxis, ideally the zidovudine treatment should be replaced by a new ARV treatment regimen. In poor resource countries PCR testing is generally not available to confirm an early diagnosis of HIV infection. ARV treatment for children should only be considered if a definite diagnosis of HIV is made.

Experience with triple therapy including a protease inhibitor in children remains limited. However early reports are encouraging and ARVs may be indicated, particularly for symptomatic children. So far only a few licensed ARVs are available in paediatric formulation: ritonavir syrup which is difficult to tolerate and nelfinavir powder which is not widely available. For the moment no indinavir syrup is commercially available. Obtaining good compliance with ARVs may be particularly difficult with children. Monitoring ARV treatment in children < 1 year old requires extra expertise. CD4 lymphocyte counts in children are much higher than in infected adults. Viral load is also generally higher in children.

8.3 HIV-2 infection

All the ARVs are effective against HIV-2 infection except the NNRTIs. ARV treatment with potentially toxic drugs is probably not appropriate in asymptomatic people with HIV-2 infection as HIV-2 infection progresses more slowly than HIV-1 infection. The monitoring of ARV treatment in people with HIV-2 infection is also complicated by the fact that there are no commercially available tests to measure viral load.

8.4 ARVs in patients with tuberculosis

In HIV infected patients being treated for tuberculosis, protease inhibitors increase the serum levels of rifampicin. On the other hand, rifampicin decreases the level of protease inhibitors. Therefore HIV infected tuberculosis patients should have double therapy without a protease inhibitor or no ARV therapy until TB therapy is complete. (Table 7). Before considering ARV treatment, patients should be screened for active tuberculosis infection, with at least a sputum examination and a chest X-ray.

TB preventive therapy (TBPT) has been shown to reduce the incidence of TB in people with HIV. The most commonly used regimen, isoniazid, is not contraindicated if patients are taking ARVs. Rifampicin containing TBPT should, however, be avoided.

In resource poor countries it is probably better to delay ARV treatment in TB patients because it complicates the TB regimen and may decrease adherence leading to inadequate TB treatment.

Table 7

Patients with active tuberculosis : Possible ARV treatment options
1. No ARV treatment during rifampicin treatment
2. Bitherapy (no PI) during rifampicin treatment
3. Tritherapy (including indinavir) but replacing rifampicin by rifabutin 300 mg/daily
4. Tritherapy with 2 NRTI + 1 NNRTI plus routine TB treatment
5. Start tritherapy including a protease inhibitor only during the 'the continuation phase' of the TB treatment with an ethambutol-isoniazid treatment regimen.

8.5 What should not be done

- Starting ARV treatment in a person in whom an HIV diagnosis has not been confirmed.
- Promising ARV treatment when its continued, long term provision cannot reasonably be guaranteed.
- Starting ARV treatment in a patient not motivated to follow such treatment or in a person who is unaware of his/her seropositivity.
- Prescribing ARV monotherapy unless it is for the prevention of perinatal HIV transmission and post exposure prophylaxis (PEP).
- Starting ARV treatment without a minimum of laboratory monitoring. In resource poor countries anaemia with haemoglobin levels 7 to 8 gram per decilitre is relatively frequent. These patients may be particularly at risk for severe anaemia during zidovudine and cotrimoxazole treatment. Chronic hepatitis caused by hepatitis B and C infections are also very prevalent in poor resource countries. ARVs are all potentially hepatotoxic and should be prescribed with caution to these patients. If these drugs are given, liver function should be monitored at regular intervals. In cases of renal insufficiency, dosage of certain ARVs such as stavudine and indinavir should be modified.
- Starting ARV treatment without providing adequate information about how and when to take the drugs, potential side effects and interactions with other drugs, when to stop the drugs, etc.
- Providing ARV treatment without the capacity to diagnose, treat or prevent opportunistic infections such as tuberculosis and toxoplasmosis (such as isoniazid for the prevention of tuberculosis, cotrimoxazole for the prevention of *Pneumocystis carinii* pneumonia and toxoplasmosis, for patients with severe immunodeficiency).
- Providing ARV treatment without capacity to meet patient's other needs such as sufficient nutritional support, adequate home care, etc.
- Continuing ARV treatment despite serious side effects; if treatment is not stopped or changed there may be irreversible damage.

9. Counselling for ARV therapy

The psychosocial aspects associated with deciding whether to start and then continue on ARV treatment are as important as the medical aspects. Counselling for ARVs is often time consuming and physicians may choose to work with a trained counsellor with specialised skills. If appropriate and informed decisions are to be made, and treatment is to be provided safely and effectively, counselling services must be available to people living with HIV/AIDS (PLHA). Those who make the decision to start ARVs will need information, support and encouragement on a regular and long term basis in order to maintain adherence to the regimen.

Where ARVs are readily available, the possibility of obtaining these treatments is an incentive to seek out counselling and testing. It has been shown that one of the main barriers to knowing one's HIV status, particularly in high prevalence areas, is the lack of perceived benefit for those who fear they might be seropositive.

Counsellors and clients will be dealing with very different psychosocial and material problems depending on the setting[3]. Where ARVs are not available or are prohibitively expensive, knowledge of these treatments may create additional stresses, for both the client and the counsellor. In such situations, counsellors will be helping clients cope with the anguish of knowing that a treatment exists which is not accessible to them. Where ARVs are provided routinely, counselling will focus on encouraging correct use, coping with a return (albeit temporary) to a more healthy and productive life, and overall emotional well-being. In settings where the client and his/her family will be investing large sums of money in the drugs, problems relating to this use of scarce resources will have to be discussed.

ARVs have received a large amount of favourable coverage in the popular press. Even in low income countries many people with HIV are knowledgeable about ARVs and have unrealistic expectations about their availability and their efficacy. It is very important for the counsellor to inform the client about the likely availability of ARVs - in both pre- and post test counselling.

After receiving a positive result, the client will need emotional support from his or her counsellor, in addition to information about many aspects of treatment and prevention. Discovering one is HIV seropositive is traumatic and marks the beginning of a difficult psychological adjustment for the client. Psychological distress and depression may be alleviated by sensitive counselling. Several counselling sessions may be needed initially for the client to cope with their positive status *in addition* to understanding the implications of ARV therapy and its monitoring. Even in countries where ARVs are readily available many patients testing seropositive will not be at a stage of disease to warrant or desire ARVs and this will need careful discussion.

Whatever decision is made about taking antiretroviral drugs, comprehensive care and social support need to be ensured on a long term basis, to identify, prevent and treat opportunistic infections and to deal with social and family problems. This may require collaboration between medical and social services in public, private and NGO sectors.

9.1 Confidentiality and sharing HIV results

The disruption of life style brought about by complicated ARV regimens should not be underestimated. Involving a partner or significant other in ARV treatment will make taking ARVs much simpler. The counsellor should encourage sharing HIV results with a partner or close relative so that the burden of the drug taking schedule can be understood and shared. The counsellor should stress the importance of informing partners of the risk of HIV transmission and taking protective action.

In many countries, women risk being abandoned if their positive status is discovered; it is frequently the partner who has infected the woman and overall it may be better not to disclose her status. The clients' own perception of the risks and benefits of the particular situation should be respected. However, many health workers feel they have a duty to inform and thereby protect a possibly uninfected partner and that this duty is greater than the duty to protect confidentiality of the client. These are ethical issues which remain unresolved. Certainly in countries where the infected and abandoned partner will *not* be left destitute and where people can easily take preventive measures, some people would feel that there would appear to be no justification for protecting confidentiality over risk of transmission of a fatal infection.

[3] for additional information see UNAIDS Technical Update November 1997 on Counselling and HIV/AIDS

9.2 Financial commitment

Discussing how the drugs are going to be paid for, is very important. In many developing countries the only option is for the patient or his/her relatives to pay for treatment. They may think that they need only take ARVs for a few months, or intermittently when they have funds. If relatives are paying, they may have to be involved - again to make decisions about willingness to pay for treatments indefinitely and the need for a consistent supply of drugs. These decisions may be very painful and difficult, but need to be thought through before embarking on treatment.

9.3 Particular challenges

Complicated drug taking schedule:

The counsellor will have to deal with many of the problems associated with complex life long therapy. A "drug time table" helps clients to organise their drug taking schedule.

Table 8 Example of a daily drug regimen

Time	Meal	Drug	Tablets	Comments
07:00		Indinavir	2	Need
		Isoniazid	1	to set alarm
08:00	meal	Zidovudine	1	
		Lamivudine	1	
		Cotrimoxazole	1	
13:00	meal			
15:00		Indinavir	2	
21:00	meal	Zidovudine	1	
		Lamivudine	1	
23:00		Indinavir	2	Forced
				to stay awake

Not a cure: The counsellor must ensure that the client is fully aware that ARV therapy is not a cure, and that the drugs must be taken for the remaining time the client has to live, or until they are too sick to take them any longer. He/she should ensure that the client understands that ARVs are new drugs and no one knows whether their short term benefits, which are often great, will continue in the long term. The counsellor needs to provide accurate up to date information about the possible positive and negative outcomes of treatment, taking into account all personal and contextual factors which may influence the outcome.

Adverse effects: Adverse effects are common in the first few weeks of ARV treatment. The counsellor should be aware of these and reassure the client that these initial adverse effects will usually lessen with time. The counsellor should also be able to help the client distinguish between potentially serious and non-serious signs and symptoms.

Disruption of life style: Dietary changes may need to be made as many of the drugs are affected by the presence and types of food eaten. Meals often have to be planned carefully around the drug regimen. This can be inconvenient and disrupt family and social life. If the counsellor can involve the family in discussions about these issues, it will help them to understand the importance of timing meals and changing routines. The counsellor may have to take time to work out a "meal and drug taking time table" that fits in with the client's and the family's life style. Client and counsellor should also discuss what to do if a dose is missed or a meal time rearranged.

Coping with "health": Taking ARVs will be for life, and once stabilised on a particular regime, the client may feel very well. This may be particularly true for people who were symptomatic prior to ARV therapy. They may be well enough to resume more of their previous lifestyle - going back to work and taking up previous hobbies or activities that were impossible before. Paradoxically, some people find the adjustment to "health" after a prolonged period of ill health difficult. Friends and family may continue to treat them as a patient despite them feeling well. The new situation and perspective will require understanding and adjustment on the part of the patient and the family.

Guilt: Some people describe feelings of guilt about taking ARVs. They may have lost partners or friends because ARVs were unavailable or could not be afforded. Many people are painfully aware of the enormous sacrifices that their friends and/or family are making to provide ARVs for them.

Coping with a "medicalised" life style: People with HIV who are asymptomatic when they start taking ARVs may resent the constraint that taking the drugs imposes on their lives. This has to be acknowledged and explored when starting ARVs. People who feel unable to embark on the strict regime that ARVs will impose on them may do better to postpone treatment.

Coping with treatment failure: Although the short term follow up of people on ARVs often results in remarkable improvement in symptomatic patients, this improvement is not universal. Furthermore, symptomatic improvement may not last long, particularly if resistance to ARVs develops, or the patient has previously been on sub-optimal ARV therapy. In developing countries, some people with HIV will put off starting ARV therapy, because of the prohibitive cost, until the last possible moment. They may by this stage be severely immunocompromised. People who have very low CD4 counts, or are terminally ill, when they start on ARV therapy tend to respond less well.

The counsellor will have to support them through the disappointment of treatment failure and balance optimism and realistic caution. Depression and despair are common when CD4 counts do not go up or weight is not gained as has been predicted or read about. This may be made worse when the client is aware of the draining of his or her financial resources into a treatment that may be futile. There may be a time when the client and counsellor will have to discuss ceasing treatment and preparing for death. There is no place for antiretroviral drugs in palliative care for severely ill patients.

9.4 Adherence issues

Combination therapy involves taking between four and 20 capsules/tablets a day depending on the regimen prescribed. Understanding how to take the drugs and the importance of not missing doses should be explained by the counsellor. The information about HIV is complicated and often confusing for clients and should be followed up with written, or clearly illustrated, instructions for future reference.

There should be open access to a counsellor for information as the need arises, and if possible, involvement of a partner or significant other, to help remind the patient about taking drugs and watching out for adverse effects. It is also important that the client understands the need for careful monitoring by a doctor and regular medical check ups.

How to improve adherence to ARV treatment?

1. Treatment decisions should be made jointly between the patient and the clinician after careful discussion of :
    - the advantages and disadvantages of ARV treatment
    - different treatment options
    - possible adverse reactions
    - the cost of the treatment
    - the need for a long term emotional and financial commitment.
2. Choice of ARV treatment regimen should take into account the life style of the patient :
    - certain patients may accept a twice daily (bd) (a regimen containing ritonavir) but not a three times daily (tds) treatment regimen (a regimen containing indinavir)
    - certain patients will be unable to store their ARV treatment (ritonavir) in a refrigerator
    - certain patients who eat at irregular time intervals may have problems taking indinavir every 8 hours on an empty stomach, 1 h before or 2 h after a meal.
3. Once an ARV treatment regimen has been chosen it should be explained very carefully:
    - how and when the drugs should be taken: written information should be provided for the patient or a family member if they are able to read. Clearly illustrated materials should be provided if the patient is unable to read.
    - what the potential adverse reactions of such treatment may be and what to do about them.
    - how and where the patient can get information about potential problems with the ARV treatment.
    - when the patient should come back for follow-up visits, and monitoring of blood tests.
    - who will help the patient to adhere to the treatment regimen: partner, another family member, a friend, a nurse. For certain patients where adherence problems can be expected, ARV treatment might need to be directly observed (DOT).
    - where to get psychosocial support.
4. Patients should be able to consult regularly with a trained counsellor to discuss all aspects of adherence.
5. There should be a reliable, long-term and regular supply of ARVs and patients should have easy access to these ARVs.
6. Communication skills of the doctor/counsellor are of great importance. Unless adequate rapport is established with the patient, adherence may be jeopardised.

9.5 ARVs must not detract from HIV prevention messages

People who take ARVs will understand that the aim of this medication is to lower the amount of virus in their blood, often to undetectable levels. They may conclude that if their viral load is very low they do not need to use protective measures to prevent HIV transmission. There have been anecdotal reports of people abandoning condom use when on ARVs. The counsellor should stress that the virus can still be transmitted and that safer sex should continue.

Alcohol and recreational drugs

There is limited information on how any of the ARVs interact with alcohol or recreational drugs. A study looking at factors that influenced HIV disease progression in long term survivors found that cannabis use, diet, and alcohol consumption, did not significantly influence disease progression. Therefore counsellors should advise that moderate alcohol intake and cannabis smoking are not contraindicated. People taking ARVs should be encouraged to lead as normal a life as possible. However, there is evidence that many recreational drugs (for example "ecstasy", amphetamines (speed) and diazepam (Valium)) interact with PIs (especially ritonavir). Any client taking recreational drugs should be encouraged to discuss this with his/her counsellor.

To the extent, however, that alcohol and any other drugs may make people less alert and responsible and therefore less able to adhere to the regimen, excessive use should be discouraged.

Support groups

Many people with HIV have found mutual support in groups of people living with HIV, very helpful. When embarking on ARV therapy it may be useful to be in contact with other people who are having similar treatments, share experiences and discuss overcoming problems associated with taking ARVs. Support groups for other medical conditions such as breast cancer have been shown to significantly improve prognosis. Clinicians and counsellors need to be aware of support groups in their area and proactively refer patients.

Counsellor support

Counselling people with HIV can be very stressful for the counsellor, especially when looking after clients and their families when a treatment fails. Regular supervision and a counsellor support group to share complicated or distressing cases provide valuable support.

Antiretroviral drugs

As all ARV drugs are relatively new, their adverse effects are still being monitored. It is very likely that additional adverse effects and drug interactions will be identified.

Nucleoside Reverse Transcriptase Inhibitors (NRTI)

(Tables 9 and 10)

Zidovudine (ZDV) often called AZT.

(Trade name Retrovir)

Zidovudine is an analogue of the nucleoside thymidine. After the drug is phosphorylated by cellular enzymes it competitively inhibits the incorporation of thymidine into the proviral DNA. The drug inhibits the prolongation of the DNA chain by preventing the addition of further nucleosides. Penetration into the cerebrospinal fluid is about 50 - 70 % of plasma levels.

Dosage and administration

250 or 300 mg bd orally
200mg tds orally
In patients with AIDS dementia complex a dosage up to 1 g a day can be considered.
Zidovudine can be taken with food or on an empty stomach but taking it with food may reduce feelings of sickness.

Adverse effects

Nausea, headache, muscle pain, skin rashes, insomnia and fatigue occur relatively frequently when starting zidovudine treatment. In most patients these complaints disappear within the first six weeks of therapy.
Haematological toxicity may develop within one month of the start of the zidovudine treatment, but generally anaemia occurs in patients with advanced disease. In patients without symptoms treated with 500-600 mg a day, haematological toxicity is rare (severe anaemia in 2% of the patients after 18 months of treatment). The mean corpuscular volume of red blood cells will increase in all patients receiving zidovudine. Long term use of zidovudine may lead to myopathy which may be preceded by an increase in creatine phosphokinase. In most patients, myopathy is reversible within 8 weeks of stopping the zidovudine therapy. Fatty liver and lactic acidosis have occasionally been reported: zidovudine should be stopped in patients with progressive hepatomegaly or if amino transferase levels rapidly increase. Bluish pigmentation of nails and mucosa is another uncommon adverse reaction.

Drug interactions

Zidovudine should not be given with stavudine because of viral antagonism. Zidovudine may cause bone marrow suppression and must be used with caution with other drugs commonly used in HIV disease such as cotrimoxazole (septrin) and gancyclovir that also cause neutropenia and anaemia.

Contraindications/precautions[4]

Do not start zidovudine in the presence of severe anaemia (haemoglobin < 7g/dl) neutropenia or leucopenia (neutrophils/leukocytes < 750/mm^3).
Combination with other potentially haematotoxic drugs such as cotrimoxazole (septrin), pyrimethamine and ganciclovir should be avoided.
Stop zidovudine if haemoglobin levels decrease below 7 g/dl, if neutrophils/leukocytes < 750/mm^3 or if persistent myalgia.

Didanosine (ddI)

(Trade name Videx)

[4] Precautions when prescribing **all** ARVs during the first trimester of pregnancy (patient must be fully informed of possible risks compared to benefits). See Module 6 for details of prescribing ARVs during pregnancy.

Didanosine is an adenosine analogue. In contrast with zidovudine and stavudine, didanosine (as well as zalcitabine and lamivudine) has a greater activity in resting peripheral mononuclear cells infected with HIV than in activated cells. Didanosine is rapidly destroyed by exposure to acid. Tablets therefore contain an antacid to prevent drug degradation and to maximise bio-availability.

Dosage and administration

200 mg bd orally for a person ≥ 60 kg
125 mg bd orally for a person < 60 kg
400mg od/250-300 mg od <60 kg
Tablets should be taken on an empty stomach. No food should be taken for 1 hour afterwards The tablets must be dispersed in water, chewed or crushed thoroughly before swallowing. The flavour of the dissolved tablets can be improved by adding clear apple juice.

Adverse effects

No haematological side effects.
Minor side effects such as nausea, vomiting, diarrhoea, skin rashes, headache, itch and lethargy have been reported but these usually settle after the first 6 weeks of treatment.
The major toxicity is a dose related, predominantly sensory, symmetric polyneuropathy. This neuropathy is generally reversible within weeks of stopping treatment. If the didanosine however is continued too long the polyneuropathy may become irreversible (the same is true for the other neurotoxic ARVs)

Another potentially serious toxicity is pancreatitis. Fatalities from ddI induced pancreatitis have been reported. Xerostomia has been reported in up to 10 % of patients. Other adverse reactions include gastrointestinal intolerance, hepatitis, hyperuricaemia and gout.

Drug interactions

The antacid in the didanosine tablets can reduce the absorption of ketoconazole and dapsone. These drugs should therefore be taken with food and several hours apart from the didanosine. Oral ganciclovir may increase the absorption of didanosine and therefore increase the risk of didanosine toxicity. ddI seriously reduces the serum level of ganciclovir. For these reasons it is best not to prescribe didanosine with ganciclovir. The use of quinolones is also contraindicated because the divalent cations in the buffer can interfere with absorption.
Didanosine may also decrease the absorption of protease inhibitors. Therefore **PIs should be taken at least 2 hours before taking didanosine.**

Contraindications/precautions

Caution is needed when didanosine is given to patients with a history of peripheral neuropathy or to patients already taking neurotoxic drugs.
Patients with advanced HIV disease, with a history of pancreatitis or who are taking other drugs or excessive alcohol that may also cause pancreatitis are at an increased risk. If the patient develops pancreas specific serum amylase levels greater than twice the normal level, stopping the didanosine should be considered.

Zalcitabine (ddC)

(Trade name Hivid)
Zalcitabine is a cytidine analogue.

Dosage and administration

0.75 mg tds orally for a person ≥ 40 kg
0.375 mg tds orally for a person < 40 kg
The absorption of zalcitabine is slightly better when taken with a meal.

Adverse effects

Polyneuropathy is more common with zalcitabine than with didanosine. It is also a dose dependent sensory, symmetric peripheral neuropathy, usually involving the lower limbs initially. The neuropathy is generally reversible after stopping treatment. If, however, the drug is not stopped in time, symptoms of polyneuropathy may persist.
Zalcitabine may cause stomatitis, mouth ulcers, nausea and vomiting, gastro-intestinal upsets, headaches and anorexia. Pancreatitis is less often observed than with didanosine.

Contraindications/precautions
Caution is needed when zalcitabine is given to patients with a history of peripheral neuropathy or to patients already taking neurotoxic drugs. Some drugs used in HIV disease can increase the risk of developing peripheral neuropathy. These include stavudine (d4T), dapsone and isoniazid, and therefore should be avoided in combination.
Caution is also needed for patients with a history of pancreatitis or who are taking other drugs or excessive alcohol that may cause pancreatitis. If a patient develops pancreas specific serum amylase levels greater than twice the normal level, stopping the zalcitabine should be considered.

Stavudine (d4T)

(Trade name Zerit)
Stavudine is a thymidine analogue. Stavudine also penetrates well into the CSF.

Dosage and administration
40 mg bd orally for a person ≥ 60 kg
30 mg bd orally for a person < 60 kg
The absorption of stavudine is slightly better when taken with a meal but it can be taken at any time.

Adverse effects
Similar peripheral neuropathy as with didanosine and zalcitabine is seen. Pancreatitis and hepatitis have also been described. There is an increased risk of pancreatitis in patients treated with pentamidine or ganciclovir. Other side effects include nausea and vomiting, fever, headache, skin rashes, diarrhoea and lethargy.

Contraindications/precautions
Caution is needed when stavudine is given to patients with a history of peripheral neuropathy or patients already taking neurotoxic drugs, in particular ddC, dapsone and isoniazid.
Caution is also needed for patients with a history of pancreatitis or who are taking other drugs or excessive alcohol that may cause pancreatitis. If a patient develops pancreas specific serum amylase levels greater than twice the normal level, stopping the stavudine should be considered.
Zidovudine should not be given with stavudine because of mutual antagonism.

Lamivudine (3TC)

(Trade name Epivir)
Lamivudine is a cytidine analogue. Rapid development of resistance is seen when used as monotherapy (causes a mutation in the HIV polymerase gene at codon 184, but lamivudine resistant strains with this mutation remain sensitive to zidovudine).

Dosage and administration
150 mg bd orally
The absorption is slightly better when lamivudine is taken with a meal.

Adverse effects
Very well tolerated. Occasionally headache, fatigue, insomnia, nausea, abdominal pain and peripheral neuropathy. Pancreatitis has been reported in children.

Contraindications/precautions
No drug interactions have been described

Table 9 : Nucleoside reverse transcriptase inhibitors

Drug Generic (trade) name	Form	Dosage	Route/conditions	Adverse events	Unit cost in US $*	Annual Cost in US $*
Zidovudine (ZDV or AZT) (Retrovir®)	T : 100, 250, 300mg A : 200 mg S : 1 ml = 10 mg	300 mg bid 100-120		headache nausea malaise anaemia neutropenia myopathy	1.5/100 mg	2,738
Didanosine (ddI) (Videx®)	T : 25, 50, 100 mg P : 150 mg	≥ 60 kg 200 mg bid < 60 kg 125 mg bid	Empty stomach Tablets must be chewed or crushed thoroughly before swallowing	polyneuritis pancreatitis abnormal liver tests	1.44/100 mg	2,102
Zalcitabine (ddc) (Hivid®)	T : 0,375, 0,750 mg	≥ 40 kg 0,750 mg tid < 40 kg 0.375 mg tid		polyneuritis pancreatitis stomatitis oral ulcers	2.4/0.75 mg	2,640
Lamivudine (3TC) (Epivir®)	T : 150 mg S : 1 ml = 10 mg	150 mg bid		well tolerated, pancreatitis in children neutropenia anaemia (when given with ZDV)	3.6/150 mg	2,572
Stavudine (D_4T) (Zerit®)	T : 30, 40 mg S = 1 ml = 1 mg	≥ 60 kg 40 mg bid < 60 kg 30 mg bid		polyneuritis pancreatitis abnormal liver tests	3.9/40 mg	2,788

T : tablet, A : ampoule, S : solution, C : capsule, P : powder

*costs at time of writing

Table 10

Interactions between nucleoside analogues and other drugs: prevention, monitoring and reducing adverse effects

	Zidovudine	Didanosine	Zalcitabine	Lamivudine	Stavudine
Pyrimethamine	Monitor haematotoxicities				
Quinolones Tetracycline Itraconazole		To absorb 2 h before the ddI			
Ketoconazole		To absorb 2 h before the ddI			Monitor hepatotoxicity
High dose cotrimoxazole	Monitor haematotoxicity			Monitor haematotoxicity	Monitor hepatotoxicity
Sulfadiazine	Monitor haematotoxicity				Monitor hepatotoxicity, neurotoxicity
Dapsone	Monitor haematotoxicity	To absorb 2 h before the ddI Monitor neurotoxicity	Monitor neurotoxicity		Monitor neurotoxicity
Pentamidine IV		Stop ddI	Stop ddC	Monitor amylase levels	Monitor hepatotoxicity amylase levels
Rifampicin					Monitor hepatotoxicity
Isoniazid		Monitor neurotoxicity	Monitor neurotoxicity	Monitor hepatotoxicity	Monitor hepatotoxicity, neurotoxicity
Amphothericin	Monitor haematotoxicity		Monitor nephrotoxicity	Monitor nephrotoxicity	Monitor neurotoxicity

Non-nucleoside Reverse Transcriptase Inhibitors (NNRTIs)

Table 11)

These compounds inhibit the HIV reverse transcriptase by binding to it non-competitively. Because they interact with a specific binding site on the enzyme any slight variation because of a point mutation may cause resistance. Therefore high level resistance develops quickly with this group of compounds if they are not given with other antiretroviral classes. The NNRTIs are inactive against HIV-2. It is currently believed that NNRTIs are only effective when used in 3 drug combinations where each of the other drugs are also new to the patient.

Nevirapine

Trade name Viramune)

Nevirapine is a dipyrido diazepinone derivative. Synergism has been shown in three drug regimens including zidovudine and lamivudine or didanosine. Nevirapine levels in the cerebrospinal fluid reach 45% of plasma concentrations.

Dosage and administration

Nevirapine can be taken with or between meals.

To evaluate whether a patient might develop an adverse reaction, it is recommended to start with 200 mg orally once a day for 2 weeks. Starting nevirapine at this lower dose supposedly reduces the chance of an adverse event. Then the dosage is increased to 200 mg orally bd.

Adverse effects

Rash, which may be accompanied by fever. Several cases of Stevens-Johnson syndrome have been reported.
Abnormal liver function tests.

Drug interactions

Nevirapine is metabolised via the cytochrome p450. Nevirapine induces cytochrome activity and may therefore decrease, serum levels of protease inhibitors.
The effectiveness of the oral contraceptive pill may be reduced when taking nevirapine.
Rifampicin may decrease nevirapine absorption.

Delavirdine

Trade name Rescriptor)

Delavirdine is a bis (heteraryl) piperazine derivative. Synergism has been shown with zidovudine, didanosine, zalcitabine or lamivudine.

Dosage and administration

400 mg tds orally.
The drug can be given with or without food. Antacids should not be administered within at least one hour of taking delavirdine.

Adverse effects

Rash (in approximately 40% of patients, usually mild). The rash usually occurs in the first 6 weeks of treatment and will disappear in 2-6 weeks if treatment is continued, however Stevens-Johnson syndrome has been reported. Other side effects include mild headache, nausea, diarrhoea, insomnia, vivid dreams and fatigue.
Abnormal liver function is observed occasionally.

Drug interactions

Delavirdine is an inhibitor of the cytochrome P450 and may therefore increase serum levels of protease inhibitors.
It should not be given at the same time as didanosine (separate administration by at least 1 hour).
Delavirdine increases serum levels of non-sedating antihistamines (terfenadine, astemizole & loratadine) and there is an increased risk of arrhythmias. Many other drugs may decrease absorption of delavirdine including sedative hypnotics (barbiturates), anti-arrhythmics, calcium-channel blockers, ergot-alkaloid preparations, vitamins, H2 antagonists, rifampicin and cisapride. Antifungals and erithromycin may increase the absorption of delavirdine.

Contraindications/precautions

Do not co-administer with rifampicin, rifabutin, phenytoin, phenobarbital carbamazepine.

Table 11

Non-nucleoside reverse transcriptase inhibitors

Drug Generic (trade) name	Form	Dosage (adults)	Route/conditions	Adverse events	Unit cost in US $	Annual cost in US $
Nevirapine (Viramune®)	T : 100 mg	200 mg qid for 2 weeks followed by 200 mg bid	with or without food	rash abnormal liver tests drug fever	4.12/100mg	6,260
Delavirdine (Rescriptor®)	T : 100 mg	400 mg tid		rash leucopenia abnormal liver tests		

T : tablet

Protease inhibitors

(Tables 12,13,14)

The enzyme protease is responsible for the cleavage of certain viral proteins. This cleavage is needed for the production of new infectious virus particles. The currently approved protease inhibitors bind to the active site of the enzyme. Protease inhibitors are metabolised by the cytochrome P450 system in the liver and many interactions are therefore possible between protease inhibitors and other drugs.

Indinavir

(trade name Crixivan)

Indinavir is a very powerful protease inhibitor. Indinavir has to be taken 3 times daily on an empty stomach. Virus isolates that are resistant to indinavir are generally cross-resistant to ritonavir. Indinavir can be stored at room temperature but in the tightly closed original container of the manufacturer because the capsules are sensitive to moisture.

Dosage and administration

800 mg orally tds. If nevirapine is associated with indinavir the dosage of indinavir should be increased to 1000 mg orally tds. Indinavir has to be taken on an empty stomach, 1 hour before food or at least 2 hours after a meal. If this is difficult - for example when taken in combination with ddI which is taken at a different time of day but also on an empty stomach - indinavir tablets can be taken with a low fat light meal.

Adverse effects

Nephrolithiasis is observed in 1-5 % of the patients. Nephrolithiasis may be a particularly frequent complication in patients treated in warm climates because of insufficient hydration.

Other side effects include : nausea, vomiting, indigestion, diarrhoea, rash, pruritis, dry skin, dry mouth, taste alteration, vivid dreams and lethargy.

Hyperbilirubinaemia occurs frequently but does not cause symptoms. Increased liver enzymes and hyperglycaemia are also seen. A redistribution of subcutaneous body fat has also been noted (lipodystrophy) and a case of coronary artery disease has been described. Delavirdine increases indinavir levels two fold.

Drug interactions

Medications that should not be given with indinavir include rifampicin, astemizole, terfenadine, cisapride, midazolam and triazolam, antifungals and anti-epileptics. Didanosine reduces the absorption of indinavir unless taken > 2 hours apart. Antacids will also decrease absorption of indinavir.

Contraindications/precautions

Precautions when prescribed during the first trimester of pregnancy (informed discussion of the possible risks compared to the benefits). Avoid with severe liver abnormalities. Patients must drink at least one and a half litres of water a day to prevent kidney stones.

Saquinavir

Trade name Invirase (SQV-HGC) and new formulation Fortovase (SQV-SGC) soft gel capsules)

Saquinavir in its new formulation has increased bioavailability making it a much more effective protease inhibitor.

Dosage and administration

Old preparation saquinavir (SQV-HGC):

The official recommended dosage is 2400 mg tds. Saquinavir should be taken with food.

Saquinavir in this preparation has low bioavailibility. It is now used in association with ritonavir or nelfinavir. (Saquinavir 2 x 400mg ritonavir 2 x 400mg) Taking the capsules with grapefruit juice increases their absorption.

New preparation saquinavir (SQV-SGC):

Has greatly enhanced bioavailability. Soft gel dosage is 1200 mg orally tds, when given as the only protease inhibitor.

When given in combination with nelfinavir 750mg orally tds the saquinavir SGC dosage should be 800 mg orally tds.

Adverse effects
Saquinavir is generally well tolerated. Spontaneous bleeding episodes have been observed in patients with HIV infection with haemophilia. Hyperglycaemia has also been reported.
Minor side effects such as diarrhoea, abdominal pain, headaches, skin rashes and parasthesia may occur.

Drug interactions
Rifampicin reduces saqinavir absorption. Anti-epileptic drugs (phenytoin and carbamazipine) and steroids (dexamethasone) also decrease saquinavir absorption.
Antihistamines such as astemizole and terfenadine should not be given with saquinavir as there is an increased risk of cardiac arrhythmia.
Antifungal drugs (ketoconazole, fluconazole, miconazole, itraconazole) may increase saquinavir absorption.
Hypoglycaemia (with some fatalities) has been reported.

Contraindications/precautions
Saquinavir is contraindicated in people with severe liver test abnormalities.

Ritonavir

(trade name Norvir)
Ritonavir is a very powerful protease inhibitor but has many side effects. When ritonavir is given as the only protease inhibitor in a combination with NRTIs, the optimal treatment dose is 600 mg orally bd. Ideally the drug has to be kept refrigerated at a temperature of 3 - 8 °C. However ritonavir can remain unrefrigerated if kept below 25 °C and used within 30 days.

Dosage and administration
The starting dose is 300 mg orally bd. This dose should be increased progressively over 10-14 days to reach an optimal dose of 600 mg orally bd. Ritonavir has to be taken with food.

Adverse effects
Nausea is very common particularly when starting treatment. Other side effects include vomiting, diarrhoea, anorexia, perioral paresthesias, peripheral paresthesias including a burning sensation of the skin, dizziness, insomnia, changes of taste and tiredness Some of these side effects are mainly observed during the beginning of the treatment and are dose dependent. They may be avoided to a certain degree by progressively increasing the dose. Other side effects include an increase in serum triglyceride levels (> 200%), uric acid and hepatic enzymes. There is an increased risk of liver toxicity in patients with underlying hepatitis E or C infection. Hyperglycaemia has been reported in patients with and without a known history of diabetes. There are reports of ritonavir causing epilepsy, orthostatic hypotension and renal insufficiency, lipodystrophies and increased bleeding in patients wit haemophilia.
As ritonavir may cause dizziness and fatigue it may interfere with some patients' ability to drive.

Drug interactions
Since ritonavir is a very potent inhibitor of the cytochrome P450 system a long list of drugs are contraindicated as concomitant treatment.
Ritonavir increases plasma saquinavir levels 50-100 fold. Therefore the combination of ritonavir 400 mg bd and saquinavir 400 mg bd is useful. This combination is generally well tolerated and the twice daily dosage is an advantage. The most frequently observed side effect is diarrhoea.
Ritonavir reduces the effectiveness of the oral contraceptive pill.

Contraindications/precautions
Severe liver function abnormalities.

Nelfinavir

(trade name Viracept)
Nelfinavir has a good bioavailability and is highly potent. The powder formulation of nelfinavir is being investigated for the treatment of children with HIV infection.

Dosage and administration
750 mg tds. If nevirapine is used in combination with nelfinavir the nelfinavir dosage should be increased to 1000 mg tds.
Nelfinavir has to be taken with food.

Adverse effects
The most commonly reported side effect of nelfinavir is diarrhoea. Other reported side effects include : nausea, elevated transaminase enzymes, hyperglycaemia and lipodystrophy.

Drug interactions
Medications that should not be given with nelfinavir include rifampicin, astemizole, terfenadine and cisapride. Rifabutin levels increase three fold with nelfinavir, so if prescribing together rifabutin levels should be reduced to half. Saquinavir increases nelfinavir levels by about 20%.

Contraindications/precautions
Avoid when patient has severe liver function abnormalities.

Future developments

Once daily preparations
There are several newer and better versions of some of the currently available drugs, which may require less frequent dosing. (For example once daily ddI and twice daily indinavir).

Combined ARVs
Preliminary data shows that the combined formulation produces similar clinical results to the conventional separate drug regimen. It is hoped that combined formulations will make adherence easier. (For example lamivudine (3TC) 150mg + zidovudine (ZDV) 300mg: trade name Combivir)

New drugs
There are currently many new ARVs undergoing clinical trials and under development.

Table 12

Protease inhibitors

Drug Generic (trade) name	Form	Dosage (adults)	Route/conditions	Adverse efffects	Unit cost in US $	Annual Cost in US $
Saquinavir (Invirase®)	C : 200 mg	600 mg tid	with food - high fat preferred	diarrhoea, nausea, abnormal liver tests hyperglycaemia	6.1/600 mg	6,540
Ritonavir (Norvir®)	C : 100 mg S : 1 ml = 80 mg	300 mg bid 3 days 400 mg bid 4 days 500 mg bid 5 days 600 mg bid by day 14	with food	bitter after taste, nausea, vomiting, diarrhoea, circumoral paresthesiasis, polyneuritis abnormal liver tests, triglycerides ↗ hyperglycaemia	11.5/600 mg	8,208
Indinavir (Crixivan®)	C : 200 mg, 400 mg	800 mg tid	1 h. before or 2 h. after a meal (or with a light meal) fluid intake >1.5 l/day	nausea, vomiting, kidney stones polyneuritis abnormal liver tests hyperglycaemia polyneuritis	4.4/800 mg	6,400
Nelfinavir (Viracept®)	T : 250 mg P : 50 mg/g 1 g/scoop	750 mg tid	with food	diarrhoea abnormal liver tests hyperglycaemia		

T : tablet, A : ampoule, S : solution, C : capsule, P : powder

Table 13

Medications that should not be used with protease inhibitors

	Saquinavir	Ritonavir	Indinavir	Nelfinavir	Potential alternatives
Analgesics	-	meperidine piroxicam propoxyphene	-		acetaminophen aspirin oxycodon
Antimycobacterial	rifabutin rifampicin	rifabutin rifampicin	rifampicin	rifampicin	rifabutin clarithromycin ethambutol
Cardiovascular (antiarrhythmic)	-	amiodarone encainide flecainide propafenone quinidine	-		very limited clinical experience
Calcium-channel blocker	-	bepridil	-		very limited clinical experience
Ergot alkaloid (vasoconstrictor)	-	dihydroergotamine ergotamine	-		-
Cold and allergy (antihistamine)	astemizole terfenadine	astemizole terfenadine	astemizole terfenadine	astemizole terfenadine	loratadine
Gastrointestinal	cisapride	cisapride	cisapride	cisapride	very limited clinical experience
Psychotropic (antidepressant)	-	bupropion	-		fluoxetene desipramine
Psychotropic (neuroleptic)	-	clozapine pimozide	-		very limited clinical experience
Psychotropic (sedative)	midazolam triazolam	clorazepate diazepam estazolam flurazepam midazolam triazolam zolpidem	midazolam triazolam	midazolam triazolam	temazepam lorazepam

Table 14

Important interactions between protease inhibitors (PI) and other drugs (OD)

Saquinavir	Ritonavir	Indinavir	Nelfinavir	Other drug	Effect
	+ +			**Analgesics** meperidine propoxyphene fentanyl pyroxicam	↗ OD pyroxicam (gastro intestinal bleeding)
+ +	+ +	+ +	+ +	**Antimycobacterials** rifampin rifabutin	↘ PI ↗ rifabutin 4x (Rit*) 2x (Ind*) ↘ PI
+	+	+	+	**Antifungals** ketoconazole	↗ PI
	+			**Antiarrhythmia** quinidine, amiodarone disopyramide lidocaine, mexiletine	↗ OD
	+			**calcium-channel blocker** bepridil	↗ OD (ventricular arrhythmia)
	+			**Beta blockers** metroprolol, pindolol propanolol, timolol	↗ OD (ventricular arrhythmia)
	+	+	+	**Anticonvulsants** carbamazepine clonazepam, phenytoin, phenobarbital	↘ PI, ↗ OD (↓ phenytoin)
	+			**Anticoagulant** warfarin	↗ warfarin
	+			**Ergot alkaloid (vasoconstrictor)** ergotamine dihydroergotamine	↗ OD

* Rit = Ritonavir
* Ind = Indinavir

	+		+	**Cold and allergy** **(antihistamine)** astemizole, terfenadine	↗ OD (ventricular arrhythmia)
	+		+	**Cold and allergy** **(antihistamine)** astemizole, terfenadine	↗ OD (ventricular arrhythmia)
	+			**Theophylline**	↘ theophylline (43%)
	+	+	+	**Gastrointestinal** cisapride	↗ cisapride (cardiac arrhythmia)
	+ +			**Antiparasites** quinine mefloquine	↗ quinine ↗ mefloquine
	+			**Psychotropic (antidepressant)** bupropion	↗ bupropion (seizures)
	+			**Psychotropic (neuroleptics)** clozapine	↗ clozapine (agranulocytosis, seizures)
 +	+ +	+ +	+ +	**Psychotropic (sedative)** diazepam triazolam	↗ OD
	+	+	+	**Anticonvulsants** carbamazepine clonazepam, fenytoin, phenobarbital	↘ PI, ↗ OD (↓ fenytoin)
	+		+	**Oral contraceptives** (ethinyl estradiol)	↘ ethinyl estradiol (40%)
+		+		**Grapefruit juice**	↘ Indinavir↗Saquinavir
	+			**metamphetamine** **"Ecstasy"**	↗ OD

Tremendous optimism has been generated by the recent development of ne antiretrovirals, particularly the triple combination therapies including one protea inhibitor, which promise a longer and better life for people living with HIV/AI (PLHA). In response to requests for the treatments from PLHA, and for policy a technical guidance from health professionals and governments, WHO, collaboration with UNAIDS, held an Informal Consultation on the Implications Antiretroviral Treatments with particular reference to low and middle incor countries, in April 1997.

Participants at the consultation, ministries of health, health professionals, PLH donors and NGOs working in HIV/AIDS have all called for technical and poli guidance for health planners and policy makers, and decision makers in traini institutions, central and district hospitals on antiretroviral treatments, as immediate follow up to the consultation.

In collaboration with UNAIDS, WHO has produced a set of nine guidan modules on the following aspects of antiretroviral treatments:

1. Introduction to antiretroviral treatments
2. Introducing antiretroviral treatments into national health systems: economic considerations
3. ARV treatments: planning and integration into health servi
4. Safe and effective use of antiretrovirals
5. Laboratory requirements for the safe and effective use of antiretrovirals
6. The use of antiretroviral drugs to reduce mother to child transmission of HIV
7. Treatments following exposure to HIV
8. Antiretrovirals: regulation, distribution and control
9. Ethical and societal issues relating to antiretroviral treatments

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