CHAPTER 16

ANTIRETROVIRAL THERAPY

Abstract

ARV is indicated in specified categories of HIV-infected individuals, prevention of mother-to-child transmission of HIV, and for PEP. ARV therapy has reversed the progress of illness in many patients with advanced disease, and prevented the progression of disease in those who are asymptomatic or relatively healthy. Keys to successful adherence include pretreatment patient education, minimum number of pills, packaging of pills, use of fixed-drug combinations, avoidance of food precautions, adherence-friendly frequency of dosing (not more than twice daily), fitting ARV therapy into the patient's lifestyle, and involvement of friends, relatives, and community members to support adherence. Pretreatment and periodic clinical and laboratory monitoring is mandatory for ARV therapy. In case of accidental occupational exposure to HIV, a specialist should explain the possible risks such as side effects of ARV drugs and benefits of PEP, and determine the likelihood of the exposed person's adherence to the prescribed regimen. Emergence of drug-resistant strains of HIV is a widespread and growing problem.

Key Words

Abacavir, Adherence, Access to treatment, Antiretroviral treatment, Darunavir, Efavirenz, Enfuvirtide, Fusion inhibitor, Indinavir, Lamivudine, Nelfinavir, Nevirapine, NNRTI, Non-nukes, Nukes, Post-exposure prophylaxis, Protease Inhibitors, Reverse transcriptase inhibitors, Ritonavir, Saquinavir, Tenofovir, Zalcitabine, Zidovudine

16.1 – INTRODUCTION

When HIV enters the blood stream through any one of the routes of transmission, it is attracted by lymphocytes that have matured in thymus and bear CD4 receptors on their surface. HIV binds to the CD4 cell receptor via its outer glycoprotein (gp 120) cover and enters the cytoplasm of the lymphocyte, where it sheds its outer coat, envelope, viral RNA, and unique enzyme *reverse transcriptase*. This enzyme gets activated and facilitates conversion of RNA into provirus DNA. This provirus DNA then creates its own mirror image and with the help of another enzyme *integrase*, integrates with the host cell genome and becomes an integral part of the host cell. This DNA copy enters the nucleus of the infected cells and multiplies and produces messenger RNA along with the multiplication of the nucleus of the host cell and is always immunologically active.

Messenger RNA directs the production of new viral particles which form into small virions with the help of another enzyme, *protease*. These small virions then bud out of the host cell and affect other cells that bear the CD4 receptor. Thus, each infected host cell becomes a "factory" of HIV that produces billions of viruses (NACO, National Guidelines).

Reverse transcriptase enzyme dominates genomic RNA. If a provirus DNA copy is not made promptly, viral replication stops. Since reverse transcriptase enzyme exists only in HIV, drugs that inhibit this enzyme will affect the virus without affecting the normal host cells. For these reasons, reverse transcriptase continues to be the *prime target* of drugs used in ARV therapy (WHO, 2003a).

16.1.1 – Public Health Aspects

The introduction of ARV treatment in 1996 in the developed countries dramatically improved morbidity and mortality rates, improved quality of life and transformed the perception of HIV/AIDS from a plague to a manageable chronic illness (Palella *et al*., 2003). ARV therapy neither destroys the virus nor cures HIV infection. The objective of ARV treatment is to retard the progress of illness in many patients with advanced disease and prevent onset of symptomatic HIV disease in asymptomatic or relatively healthy HIV-positive individuals (Harries *et al*., 2004; Wig, 2002).

ARV treatment improves quality of life and offers hope to HIV-affected individuals and encourages voluntary disclosure of HIV infection in order to receive ARV treatment. Appropriate ARV treatment is a *life-saving tool* at the individual level and also an important *public health intervention* for retarding the progress of the HIV epidemic (John, 2001; Clinton, 2003).

16.1.2 – Art: Principles and Perspectives

The cost of treatment of tuberculosis, leprosy, and malaria is borne by the Government. Treatment for these diseases is a *public health intervention* to reduce the incidence of disease. The same principle should also apply to ARV treatment for HIV/AIDS. It is necessary to decide what clinical conditions signal the need for starting ARV treatment. As long as an HIV-infected individual has good quality of life, ARV treatment can be withheld. This makes sound medical and economic sense. When opportunistic infections, such as tuberculosis are diagnosed, the immediate step is to initiate specific treatment against these diseases and not to start ARV treatment. Currently the decision-making process for starting ARV treatment is left to an individual physician's own criteria. A mechanism, such as a decision by a panel of three physicians, is necessary to ensure that strict adherence to criteria for starting ARV treatment are developed and validated through research. Such a provision already exists in India: for MTP between 12 and 20 weeks gestation, the opinion of two specialists is necessary (John, 2004).

Since CD4 cell counts may not be available everywhere, it is necessary to decide on the use of simple tests, such as haemoglobin, hematocrit, total lymphocyte count, for monitoring ARV treatment. Currently it is possible to computerise clinical and laboratory data of each patient who is started on ARV treatment, with a programmed alert for timely follow-up. ARV treatment protocols and guidelines for monitoring should be made available to all physicians in private and public sector to prevent the "therapeutic anarchy" that currently prevails in case of antitubercular treatment. Likewise, every medical college and postgraduate training centre in the country ought to receive ARV treatment protocols and guidelines for monitoring to ensure nationwide uniformity of teaching curriculum for tomorrow's doctors (John, 2004).

16.1.3 – Prerequisites

Successful implementation of ARV treatment requires political commitment, diagnosis and registration of patients, standardised treatment regimens, regular and reliable supply of ARV drugs, and provision for monitoring and evaluation of the programme. ARV drugs must be used in standardised multidrug combinations to prevent development of drug resistance (Harries *et al*., 2004).

16.1.4 – Classification of Antiretroviral Drugs

None of the currently available ARV drugs can kill HIV. ARV drugs belong to the following main classes; they act at different stages of the life cycle of HIV
- Reverse transcriptase inhibitors (RTIs or "nukes") – Appendix 2
- Non-nucleoside RTIs (NNRTIs or "non-nukes") – Appendix 6
- Protease Inhibitors (PIs) – Appendix 4
- Attachment and Fusion Inhibitors – Appendix 5
- Immune stimulators – Appendix 6
- Integrase inhibitors – Appendix 6
- Antisense drugs – Appendix 6
- Maturation inhibitors – Appendix 6
- Zinc finger inhibitors or zinc ejectors – Appendix 6

RTIs or "nukes" are further subdivided into two groups: (a) Nucleoside analogue RTIs (NsRTIs), and (b) Nucleotide analogue RTIs (NtRTIs).

16.2 – CLINICAL AND LABORATORY MONITORING

16.2.1 – Baseline Pretreatment Clinical Assessment

For all the four recommended first-line regimens (the interested reader may read details from reference: WHO, 2003a), the baseline clinical assessment should include:
- Documentation of past medical history.
- Identification of coexisting medical conditions such as tuberculosis, pregnancy, and major psychiatric illnesses, and documentation of concomitant

medications including traditional therapies. Active tuberculosis is to be managed in accordance with national tuberculosis control programmes.
- Recording the patient's weight and assessing his or her readiness for ARV treatment.
- Identifying current symptoms and physical signs.
- Staging of HIV disease (WHO, 2003a).

16.2.2 – Periodic Clinical Assessment During Treatment

This includes assessment for signs and symptoms of potential drug toxicities, patient's adherence to therapy, response to therapy, recording body weight, and basic laboratory monitoring (see below).

16.2.3 – Laboratory Monitoring

The WHO has recommended a three-tiered system of laboratory monitoring in resource-limited settings (WHO, 2003a).

16.2.3.1 – Primary health care centres (Level 1)

Rapid HIV antibody testing, assessment of haemoglobin levels (if ZDV is being considered for use), pregnancy testing, and sputum smear microscopy for tuberculosis.

16.2.3.2 – District hospitals (Level 2)

Rapid HIV antibody testing and capability to resolve indeterminate rapid HIV antibody test report by second serological method, complete and differential blood count, CD4 cell count, serum alanine amino transferase (ALT), pregnancy testing, and sputum smear microscopy for tuberculosis.

16.2.3.3 – Regional referral centres (Level 3)

Rapid HIV antibody testing, complete and differential blood count, CD4 cell count, serum ALT, pregnancy testing, sputum smear microscopy for tuberculosis, assessment of viral load, and full serum chemistry including electrolytes, renal function, liver enzymes, and lipids (WHO, 2003a).

16.3 – ARV THERAPY FOR ADULTS AND ADOLESCENTS

As per recommendations of the WHO, in resource-limited settings, adults and adolescents should be started on ARV treatment when they have confirmed HIV infection and one of the following conditions.

16.3.1 – In Settings where CD4 Testing is Available

- WHO Stage IV HIV disease, irrespective of CD4 cell count.
- WHO Stage III HIV disease, with a CD4 cell count of less than 350 cells per μL to assist decision-making. This includes HIV wasting, chronic diarrhoea of

unknown aetiology, prolonged fever of unknown aetiology, pulmonary tuberculosis, recurrent invasive bacterial infections or recurrent/persistent mucosal candidiasis.
- WHO Stage I, or Stage II HIV disease, with a CD4 cell count of less than 200 cells per μL.

The precise CD4 level above 200 cells per mm^3, at which ARV treatment should be initiated, has not yet been established (WHO, 2003a). However some recommendations suggest that the treatment should not be started until the CD4 T-lymphocyte count falls below 350 cells per mm^3 or viral load exceeds 50,000 copies per mL. These recommendations are based on the risk of developing AIDS within 6 years without treatment (Kelly, 2002).

16.3.2 – In Settings where CD4 Testing Facilities are not Available

The presence of a *total lymphocyte count* of 1,200 cells per mm^3 or below can be used as a *substitute indication* for treatment in the presence of symptomatic HIV disease. The total lymphocyte count is not useful indicator in an asymptomatic patient. Thus, in the absence of CD4 testing facilities, asymptomatic HIV patients (WHO Stage I) should not be started on ARV treatment because currently no other reliable marker is available in resource-limited settings.
- WHO Stage IV HIV disease, irrespective of total lymphocyte count.
- WHO Stage III HIV disease, irrespective of total lymphocyte count. This includes HIV wasting, chronic diarrhoea of unknown aetiology, prolonged fever of unknown aetiology, pulmonary tuberculosis, recurrent invasive bacterial infections or recurrent/persistent mucosal candidiasis.
- WHO Stage II HIV disease, with a total lymphocyte count of less than 1,200 cells per mm^3.

Assessment of viral load (plasma HIV-1 RNA levels) is not necessary to start therapy and is not recommended as a routine test by the WHO (2003a).

16.3.3 – First-Line Regimens (Adults and Adolescents)

In order to develop accessible ARV treatment programmes, countries with resource limitations need to standardise treatment regimens, select a first-line regimen, and select a limited number of second-line regimens. In such settings, patients who cannot tolerate or fail the first-line and second-line regimens will be referred (for individualised care) to specialists in HIV medicine (WHO, 2003a).

16.3.4 – Criteria for Selecting First-Line Regimens

These include availability, storage requirements, and cost of ARV drugs, especially availability in fixed-dose combinations (FDCs) or as co-blister packs, availability of potency and profile of adverse reactions, laboratory monitoring requirements, potential for maintaining future treatment options, availability of data on expected patient adherence, coexisting conditions such as metabolic

diseases and infections, pregnancy or risk of pregnancy, concomitant use of medications and potential drug interactions, and potential for infection with a strain of HIV with reduced susceptibility to one or more ARV drugs (WHO, 2003a). "Holding regimens" contain drugs such as lamivudine (3TC) help in keeping the virus "handicapped" with multiple mutations, so that it multiples slowly (Fact Sheet 408, 2006).

16.3.5 – Changes in First-Line Regimen

ARV drugs may need to be changed due to treatment failure or drug toxicity. This has been termed "salvage therapy" (Fact Sheet 408, 2006). When toxicity is related to an identifiable drug in the regimen, the offending drug can be replaced with another drug that does not have the same adverse effects. Protease inhibitor-based regimens are primarily reserved for second-line therapy. Though these regimens have proven clinical efficacy, they have significant interactions with other drugs such as rifampicin. A functioning cold chain is essential for ritonavir (RTV)-boosted regimens. Co-formulations of PIs with NNRTIs are not available. Therefore, protease inhibitor-based regimens may be considered for first-line regimens where prevalence of NNRTI resistance in the community is more than 5–10 per cent (WHO, 2003a).

Viral Load: Within 2–4 weeks after starting ARV therapy, the HIV-RNA should be preferably less than 10,000 copies per mL, i.e. one log reduction in viral load or more. If HIV-RNA is more than 100,000 copies per mL or the reduction in viral load is less than 0.5 logs, ARV therapy should be adjusted by adding or switching drugs. Viral loads should be repeated every 4–6 months during periods of clinical stability. If viral load returns to 0.3–0.5 logs of pretreatment levels, then ARV treatment is no longer working and should be changed.

CD4 Cell Count: Within 2–4 weeks of starting ARV treatment, CD4 cell count should increase by at least 30 cells per mm^3. If this is not achieved, ARV treatment should be changed. CD4 cell counts should be obtained every 3–6 months during periods of clinical stability and more frequently in case of symptomatic HIV disease. If CD4 cell count drops to base line (or below 50 per cent of increase from pretreatment levels, then ARV treatment should be changed.

16.3.6 – Treatment Failure

This can be assessed *clinically* by disease progression, *immunologically* by CD4 cell counts, and *virologically* by measuring viral loads. The WHO recommends the use of clinical criteria, and, where possible, CD4 count criteria to define treatment failure. Testing for drug resistance will not be routinely available in resource-limited settings in the foreseeable future. In developing countries, recognition of treatment failure will be delayed when based on clinical criteria and/or CD4 criteria alone. Such a delay will provide greater opportunity for evolution of drug resistant mutations before the ARV drug regimen is changed (WHO, 2003a).

16.3.7 – Clinical Signs of Treatment Failure

Occurrence of new opportunistic infection or malignancy denotes clinical progression of disease. This should be differentiated from *immune reconstitution syndrome* (IRS). This condition is characterised by the appearance of signs and symptoms of an opportunistic disease as an inflammatory response to a previously subclinical opportunistic infection. IRS is seen a few weeks after initiation of ARV treatment in patients with advanced immune deficiency. Its occurrence may lead to development of atypical presentations of some opportunistic infections. *Recurrence* of a previous opportunistic infection is also a sign of treatment failure. However, recurrence of tuberculosis may not represent progression of HIV disease since reinfection may occur. Hence clinical evaluation is essential. Onset or recurrence of WHO *Stage III conditions* may also indicate treatment failure. If the patient is asymptomatic and treatment failure is defined using CD4 cell count alone, a confirmatory CD4 cell count should be considered (WHO, 2003a).

16.4 – ARV THERAPY FOR WOMEN

While choosing a regimen for women with childbearing potential or who are pregnant, there is likelihood that the ARV drugs may be administered in the first trimester of pregnancy, before pregnancy is diagnosed. Efavirnez (EFV), a NNRTI, should be avoided in such women because of its potential for teratogenicity. However, EFV remains a viable option in those women for whom effective and reliable method of contraception can be assured (WHO, 2003a).

The recommended first-line regimen for women with childbearing potential or pregnant women is *Stavudine* (*d4T*) *or Zidovudine* (*ZDV*) + *Lamivudine* (*3TC*) + *Nevirapine* (*NVP*). For pregnant women, it is desirable to start ARV treatment after the first trimester. However, for severely ill women, the benefit of early ARV treatment outweighs any potential foetal risks and ARV treatment should be started in such cases. Women receiving efavirenz (EFV)-containing regimens, who become pregnant, should continue their treatment; with the exception that EFV is replaced by NVP (WHO, 2003a).

The dual NRTI combination of d4T/didanosine or di deoxy inosine (ddI) should be avoided in pregnancy due to its potential for lactic acidosis in pregnant women. Symptomatic NVP-associated hepatotoxicity or serious rash is more frequent in women (as compared to men) and is more likely in women with high CD4 cell counts (more than 250 cells per mm^3). PIs can lower the blood levels of oral contraceptives. Therefore, women receiving PIs should use additional or alternative contraceptive methods, such as consistent use of condoms to avoid pregnancy (WHO, 2003a).

16.4.1 – Prevention of Mother-to-Child Transmission

ARV regimen for HIV positive pregnant women should be started before and during delivery, and also within 48 hours of the delivery. ARV drugs act mainly by reducing viral load in the mother, so less quantity of virus is transferred to the

infant, and preventing fixation of HIV in the child's tissues. An issue of concern is the potential impact of NVP prophylaxis used for PMTCT on the subsequent treatment of the mother and her infant. Until more information is available, women who have received single dose prophylaxis with NVP or 3TC for PMTCT should be considered eligible for NNTRI-based regimens (WHO, 2003a).

16.5 – ARV THERAPY FOR INFANTS AND CHILDREN

It is difficult to make a laboratory diagnosis of HIV infection in infants and children aged *below 18 months* due to persistence of maternal antibodies. The WHO recommends initiation of ARV treatment if the infant/child has virologically proven infection (using either HIV-DNA PCR, HIV-RNA assay, or immune-complex dissociated p24 antigen) and has:

- WHO Paediatric Stage III Disease: AIDS-defining opportunistic conditions, severe failure to thrive, progressive encephalopathy, malignancy, meningitis, irrespective of CD4 cell count.
- WHO Paediatric Stage II Disease: chronic diarrhoea, severe persistent or recurrent candidiasis, weight loss, persistent fever, severe recurrent bacterial infections, generalised lymphadenopathy, with consideration of using CD4 cell count less than 20 per cent to assist in decision-making.
- WHO Paediatric Stage I: (i.e. asymptomatic) and CD4 cell count less than 20 per cent. WHO Stage I should be treated *only if* facilities for CD4 cell count are available (WHO, 2003a).

The current WHO staging system for paediatric HIV infection was developed many years ago. Many of the clinical symptoms in Paediatric Stage II and Stage III are not specific for HIV infection. These symptoms may overlap with those seen in HIV-negative children in resource-limited settings. Till the revision of the classification system, the existing classification system is to be used in resource-limited settings for defining parameters for initiating ARV treatment (WHO, 2003a).

Breastfed infants are at risk of HIV infection during the entire period of breastfeeding. A negative virologic or antibody test at one age does not exclude the child becoming infected at a later time if breastfeeding is continued. The penetration of ARV drugs into human breast milk has not been quantified for most of these drugs. Some ARV drugs like NVP are present in breast milk, but the quantity of the drug that would be ingested by the infant through breast milk would be less that the required therapeutic levels. Ingestion of *subtherapeutic levels* of ARV drugs through breast milk may lead to development of resistance. Therefore, if a breastfed infant is sufficiently ill to require ARV treatment, standard paediatric doses of ARV drugs should be started, irrespective of whether the mother is receiving ARV treatment (WHO, 2003a).

16.5.1 – Recommended First-Line ARV Regimens in Infants and Children

Dosing in children is based on *body surface area* or *body weight* in order to avoid the risk of underdosing and the development of resistance. The formula (Harries

et al., 2004) for calculating BODY SURFACE AREA (in m^2) is – $BODY\ SURFACE\ AREA\ (in\ m^2) = \sqrt{\{(HEIGHT\ in\ centimetres \times WEIGHT\ in\ kg)/3600\}}$.

The doses must be adjusted as the child grows. Non-expert personnel need to be provided with a table of drug doses to ensure administration of correct doses. Regimens chosen for children should be similar to those used by the parents in order to avoid different timings and thus improve adherence (WHO, 2003a).

Some ARV drugs are available in specially designed formulations for paediatric use. But, these formulations may not be widely available in resource-limited settings. Use of tablets that require cutting up (especially unscored tablets) can result in under- or overdosing, leading to either drug resistance or toxicity (WHO, 2003a).

16.5.2 – Clinical and Laboratory Monitoring in Infants and Children

The parameters for laboratory monitoring for infants and children on ARV treatment are the same as for adults and adolescents. In addition to the clinical parameters recommended for adults, the *clinical monitoring* in infants and children should include growth and nutritional status, developmental milestones, and neurological symptoms (WHO, 2003a). Salient *clinical signs of response* to ARV treatment in children include improvement in growth and achievement of developmental in children, decreased frequency of bacterial infections, oral thrush, other opportunistic infections, and/or improvement in neurological symptoms.

16.5.3 – Changing ARV Therapy Regimens in Infants and Children

The indications and principles for changing ARV treatment in infants and children is the same as for adults and adolescents. Management of drug toxicity is also the same. If toxicity is related to an identifiable drug, the offending drug is replaced with one that does not have the same side effects (WHO, 2003a).

16.5.4 – Clinical Signs of Treatment Failure

Clinically, treatment failure is determined by lack of growth (or decline in growth) in children, who show initial response to treatment; loss of neurodevelopmental milestones or development of encephalopathy; occurrence of new opportunistic infection or malignancy indicating disease progression; and recurrence of previous opportunistic infections, such as oral candidiasis, that is refractory to treatment (WHO, 2003a).

16.5.5 – CD4 Cell Criteria for Treatment Failure

- Return of CD4 cell percentage (for children older than 6 years of age, of absolute CD4 cell count) to pretreatment baseline levels, or below, in absence of other concomitant infection to explain transient decrease in CD4 counts.

- More than 50 per cent decrease of CD4 cell percentage (for children older than 6 years of age, of absolute CD4 cell count) from peak treatment levels, in absence of other concomitant infection to explain transient decrease in CD4 cell counts (WHO, 2003a).

16.6 – ARV THERAPY FOR TUBERCULOSIS PATIENTS

Treatment of tuberculosis is a *central priority* and should not be compromised by ARV treatment. The optimal time for initiating ARV treatment in tuberculosis patients is *not known*. ARV treatment may be *life saving* in patients with advanced HIV disease, during the first 2 months of antitubercular treatment, since case fatality rates are high (WHO, 2003a). The WHO recommendations (revised in 2003) are outlined in Table 1.

Though clinical evidence supporting treatment recommendations are incomplete, the *first-line* ARV treatment regimen for tuberculosis-HIV co-infection is: (*Stavudine or Zidovudine*) + *Lamivudine* + *Efavirenz* (600 or 800 mg per day). Management of tuberculosis-HIV co-infection is complicated by the need to achieve patient acceptance of both the diagnoses, interaction of rifampicin with NNRTIs and PIs, pill burden, problems related to adherence, and drug toxicity (WHO, 2003a).

16.7 – ARV THERAPY FOR INJECTING DRUG USERS

HIV programmes need to ensure that this vulnerable subgroup in the HIV-infected population have access to life-saving ARV therapy and integrate treatment of drug dependence with HIV care. In such settings, directly observed

Table 1. Options for HIV-tuberculosis co-infection (WHO, 2003a)

CD4 Cell count	Recommended options and regimen
<200 per mm^3	• Start tuberculosis treatment. • Start antiretroviral therapy as soon as tuberculosis treatment is tolerated (between 2 weeks and 2 months) – recommend EFV-containing regimens.[a]
200–350 per mm^3	• Start tuberculosis treatment. • Start antiretroviral therapy after initial phase of tuberculosis treatment. Start earlier is severely compromised. • Consider antiretroviral therapy regimens – EFV-containing[a] (OR) NVP-containing.[b]
>350 per mm^3	• Start tuberculosis treatment and monitor CD4 counts. • Defer antiretroviral therapy.
CD4 cell counts – facility NOT available	• Start tuberculosis treatment. • Consider antiretroviral therapy.

[a] Efavirenz (EFV) is contraindicated in pregnant women and women of childbearing potential without effective contraception.
[b] Nevirapine (NVP) may be used in case of rifampicin-free continuation phase of tuberculosis therapy.

ARV therapy is a feasible option to ensure adherence. A number of ARV drugs are being explored for once daily use so that it can be considered for *directly observed therapy* (WHO, 2003a). The clinical and immunological criteria for starting ARV therapy in IDUs are the same as those in the general recommendations.

Problems in Treating Drug Users: Lifestyle instability in drug users affects adherence to ARV therapy. ARV drugs such as EFV, NVP, and RTV reduce plasma levels of methadone, leading to signs of opiate withdrawal. Patients receiving methadone along with ARV therapy should be monitored for signs of withdrawal and their methadone dose may have to be increased to alleviate withdrawal symptoms (WHO, 2003a).

16.8 – ADHERENCE TO ARV THERAPY

High levels of adherence to ARV therapy (more than 95 per cent) are desirable to maximise benefits such as improved virological and clinical outcomes, avoid drug resistance, and ensure durability of effect of ARV therapy (WHO, 2003a).

16.8.1 – Pretherapy Education

Peer counsellors can help in educating the patient on HIV and its manifestations, benefits and side effects of ARV medications, mode of taking the medications, and importance of not missing any dose.

16.8.2 – Ensuring Adherence during Therapy

Once treatment has begun, the keys to *successful adherence* to ARV therapy need to be remembered. These include minimum number of pills, such as fixed drug combinations, packaging of pills (such as co-blister packs), avoidance of food precautions, daily frequency of dosing not exceeding twice daily, fitting ARV therapy into the patient's lifestyle, and involvement of friends, relatives, and community members in support of the patient's adherence. Adherence should be assessed during visits to health centres. Home visits are useful. *Family-based care* is advised when more than one family member (especially mother and child) is HIV-infected. Support (from friends, relatives, community members) is essential for ongoing adherence since the duration of ARV therapy is lifelong duration (WHO, 2003a).

On 12 July 2006, the FDA of the United States announced the approval of Atripla, a FDC containing EFV, emtricitabine, and tenofovir (TDF) disoproxil fumarate for treatment of HIV-1 infection in adults. Atripla is the first one-pill, once-a-day ARV product that simplifies the treatment regimen for HIV-1 infected adults and has the potential to improve adherence of patients. Since May 2004, the FDA has approved seven co-packaged drugs or fixed drug combinations (FDA, 2006).

16.8.3 – Other Strategies for Ensuring Adherence

Though it has been suggested that cost sharing may assist adherence, studies from African countries indicate that cost sharing is detrimental to long-term adherence. Introduction of DOT, or its modifications, is a challenging task since DOT is resource-intensive and is difficult to sustain for the lifelong duration of ARV therapy. This approach may be useful for certain groups and for early patient training and has been successfully implemented in Haiti (John, 2004). Other strategies include using mobile vans to reach rural communities, ensuring regular and reliable supply of ARV drugs, and providing resources for culturally acceptable adherence programmes (WHO, 2003a).

16.8.4 – Community-Based Buyers' Club

The Thai Network of people living with HIV/AIDS (TNP+) established the Buyers' Club in October 2000 in partnership with local NGOs and Médecins Sans Frontières (MSF) with the objective of increasing access to a limited range of essential ARV drugs. Generic drugs were purchased directly from Thailand's Government Pharmaceutical Organisation. TNP+ has successfully negotiated a preferential price for EFV from the manufacturer Merck Sharp and Dohme. Members of Buyers' Club get selected ARV drugs along with suitable information on treatment, importance of adherence and follow-up of those who miss a prescription, and coping with side effects. The concept of Buyers' Club has spread to other countries such as Japan, Iran, Malaysia, and China (Kreudhutha *et al*., 2005).

16.8.5 – Measuring Adherence

The numerous treatment challenges posed by ARV treatment include lifelong duration of treatment, pill burden, frequent dosing intervals, food restrictions, and adverse effects. Over 95 per cent adherence is required for viral suppression (Nwokike, 2005). Ensuring free medicines does not guarantee adherence. National ARV programmes need to develop adherence measurement and monitoring systems which are built into the national treatment protocols. Adherence measurement tools include:

1 *Pill count and/or estimation of volume of liquid medications during each visit* – a zero tolerance policy needs to be adopted viz. missing one dose in a four dose-per-day regimen translates to non-adherence for that day (Nwokike, 2005).
2 *Pill identification tests* – asking patients to identify their own pills from other pills that also include look-alike pills (Parienti *et al*., 2001).
3 *Issuing monthly pill calendars*.
4 *Adherence partner* – having an adherence partner has been shown to be the most crucial factor that promoted adherence (Nwokike, 2005).
5 *Using a 7-day recall questionnaire* (Liu *et al*., 2001) – However, this method may overestimate adherence.

16.8.6 – Adherence During Pregnancy and Post-Partum Period

Pregnancy-associated morning sickness, gastrointestinal upsets, and fears about potential effects on foetus may complicate ARV therapy. Post-partum physical changes and demands of caring for a newborn may compromise maternal drug adherence. Therefore, culturally appropriate adherence mechanisms need to be developed (WHO, 2003a).

16.8.7 – Adherence in Children

Adherence in children is complicated by disruption of the family unit by health or economic reasons. Keys to successful adherence to ARV therapy include family-based treatment programmes, wide availability of improved paediatric formulations, and matching of paediatric and adult regimens (i.e. frequency of dosing for mother and child should be similar) (WHO, 2003a).

16.8.8 – Innovative Methods for Ensuring Adherence

Innovative methods for ensuring adherence in antitubercular treatment may also be replicated in case of ARV therapy. Haiti has successfully experimented with administration of ARV drugs under direct observation or supervision – similar to directly observed treatment for tuberculosis (John, 2004). Since the duration of ARV therapy is lifelong, ensuring adherence may require many more innovative methods, as compared to that for antitubercular treatment.

Cape Town (South Africa) has 71 per cent cell phone usage. In a pilot project, Dr. David Green (www.compliance.za.net) used a freely available open source operating system, web server, and a database of patients receiving antitubercular treatment. Each day, the computer server sent half-hourly short messaging service (SMS) messages to remind patients to take their treatment. A variety of 800 other messages (jokes, lifestyle tips) were also on the database. Messages were changed daily to relieve boredom. The Cape Town Health Authority paid the equivalent of US$1.30 per patient per month to run the SMS reminder service. Out of more than 300 patients who were involved in the pilot project, there were only five treatment failures. WHO has singled out this novel scheme as an example of best practice (WHO, 2003b).

16.9 – SURVEILLANCE OF DRUG RESISTANCE

The WHO recommends the establishment of HIV drug resistance sentinel surveillance system to detect potential drug resistance at population level and to modify treatment regimens in view of the available information. To begin with, the prevalence rate of drug resistance is to be established in HIV-infected persons who have not received ARV therapy. After this, HIV-infected patients on ARV therapy (especially those diagnosed with treatment failure) should be

monitored (WHO, 2003a). Drug susceptibility tests for ARV drugs is based on phenotypic and genotypic assays.

Phenotypic Assays: Phenotypic assays can only be used for cultivable viruses. These assays indicate whether a particular strain of a virus is sensitive or resistant to an ARV drug by determining the concentration of drug needed to inhibit growth of the virus in vitro. In case of HIV, plaque reduction assays may not be suitable since all HIV strains do not produce plaques in cell culture.

Genotypic Assays: Molecular techniques such as polymerase chain reaction and ligase chain reaction are used to assay mutations associated with drug resistant viruses. Being tedious, these assays are not suitable for routine diagnostic laboratories. Since HIV mutates rapidly, resistant strains may have merged in the early stages of infection.

16.10 – LIMITATIONS OF ARV THERAPY

16.10.1 – Limitations of Therapy

Due to the severity of the HIV epidemic, many ARV agents have been speedily licensed, often with little knowledge about their long-term safety (Wig, 2002). Emergence of drug-resistant strains of HIV is a widespread and growing problem (Durant *et al*., 1999). The objective of ARV therapy is the long-term suppression of viral load. However, studies have revealed that even in successfully treated patients with extremely low (or undetectable) plasma HIV-1 RNA levels, HIV persists in sanctuaries where the drug cannot reach, or continues to exist in a *latent form* on which the drugs have no effect (Wong *et al*., 1997). HIV has also been detected in the semen of patients who are on ARV therapy, without detectable HIV in the blood (Zhang *et al*., 1998). Testes are a reservoir of HIV and the viral load in blood and semen is possibly different (Coombs *et al*., 1998). Vasectomy in HIV-infected individuals does not reduce the quantity of HIV in the ejaculate, as most of the seminal fluid and cell-free HIV concentrate at a point proximal to the site of vasectomy (Zhang *et al*., 1998). The persistence of latent HIV infection despite therapy for the prescribed duration suggests that *lifelong* treatment is necessary. The currently available drugs are expensive and difficult to tolerate for prolonged periods (Furtado *et al*., 1999). In patients whose plasma HIV-1 RNA levels had been suppressed by ARV drugs to below undetectable levels, the plasma HIV-1 RNA levels invariably rebounded, within 3 weeks after the cessation of therapy (Harrigan *et al*., 1999).

Problems in ARV treatment include intolerance of ARV drugs due to adverse reactions, poor adherence of patients and resulting emergence of drug resistance, use of non-standardised regimens, need for careful monitoring to evaluate response to treatment, high rate of HIV turnover and spontaneous mutation, and drug-induced selective pressure (Harries *et al*., 2004; Potter *et al*., 2004; NIAID, 2005).

16.10.2 – Limited Access to Antiretroviral Drugs

Research projects and programmes provide free ARV drugs only to HIV-infected individuals who meet inclusion criteria and live in a defined geographic area. In some countries, government programmes provide free ARV treatment at select institutions located in major cities. Even if treatment is free of cost, patients or their families have to bear costs of transport and possibly loss of daily wages of the accompanying family member. The dilemma faced by health care providers is how to tell impoverished patients that they must travel to specific government treatment centres in order to avail of free treatment (Whyte *et al*., 2005).

In many resource-poor countries, prices of ARV drugs have fallen drastically, bringing fee-for-treatment within reach of more families. But for poor families, the decision to start ARV treatment involves painful prioritising. Supporting long-term ARV treatment for one family member would mean not being able to help another family member with money for education or some other important career goal. The situation gets worse when more than one family member is HIV-infected. When resources are scarce, the dilemma faced by family members is which family member is to be financially supported for ARV treatment. Even when a decision is made to initiate treatment, it is difficult to maintain the regimens for prolonged periods in the face of many other needs. The main reason for discontinuing treatment is economic. Families may have to make difficult choices that may influence adherence and hence these choices should be discussed during pretreatment counselling. Unequal access to ARV treatment poses questions of social justice particularly in poor nations where people cannot afford to buy drugs even at reduced prices and ultimately, unequal access may also influence adherence to treatment (Whyte *et al*., 2005).

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APPENDIX 1

READY RECKONER

Table 2. Dosages for adults and adolescents (WHO, 2003a)

Group	Drug	Dose
Nucleoside reverse transcriptase inhibitors (NsRTIs)	Abacavir (ABC)	300 mg twice daily
	Didanosine (ddl)	400 mg once daily; (250 mg once daily if <60 kg); 250 mg once daily if administered with Tenofovir
	Lamivudine (3TC)	150 mg twice daily (or) 300 mg once daily
	Stavudine (d4T)	40 mg twice daily; (30 mg twice daily if <60 kg)
	Zidovudine (ZDV)	300 mg twice daily
NtRTI	Tenofovir disopril fumarate (TDF)	300 mg once daily*
NNRTIs	Efavirenz (EFV)	600 mg once daily
	Nevirapine (NVP)	200 mg once daily for 14 days, then 200 mg twice daily
Protease Inhibitors (PIs)	Indinavir/ritonavir (IDV/r)	800/100 mg twice daily
	Lopinavir/ritonavir (LPV/r)	400/100 mg twice daily (533/133 mg twice daily when combined with efavirenz or nevirapine)
	Nelfinavir (NFV)	1250 mg twice daily
	Saquinavir/ritonavir (SQV/r)	1,000/100 mg twice daily (or) 1,600/200 mg once daily

* TDF + ddl: drug interaction necessitates dose reduction of ddI.
Note: The dose of each drug may vary if anti-retroviral drugs are combined.

APPENDIX 2

NUCLEOSIDE ANALOGUE RTIs (NSRTIs)

RTIs (or "nukes") were the first ARV drugs. ZDV was approved for use in the United States in 1987 (Fact sheet 402, 2006). These drugs are analogues of nucleosides. ZDV is an analogue of thymidine; ddI is converted to an analogue of adenosine; and zalcitabine or di deoxy cytidine (ddC) is an analogue of cytidine. NsRTI are phosphorylated intracellularly to triphosphate, which inhibits synthesis of the DNA chain by reverse transcriptase enzyme (Lewin *et al*., 1997). The dose of each drug may vary if ARV drugs are combined.

[A] ZIDOVUDINE (ZDV)

Synonym: Di deoxy thymidine or azidothymidine (AZT)

Pharmacology

The drug is a NsRTI and is active against both HIV-1 and HIV-2. It is indicated in adults infected with HIV. It prevents infection of uninfected cells and limits viral replication in infected cells. However, the drug does not eradicate established infection. Ribavarin and d4T antagonises the ARV action of ZDV (Harries *et al*., 2004). Resistance to ZDV is seen mostly after at least 6 months of therapy and may decline on withdrawal of the drug (Land *et al*., 1992; Mulder *et al*., 1994). Resistance develops more rapidly in patients with lower CD4 cell counts. In HIV-infected pregnant women, ZDV treatment reduces the risk of transplacental transmission by up to 75 per cent (Connor *et al*., 1994). However, combination therapy is superior to ZDV monotherapy (Lewin *et al*., 1997).

Bioavailability on oral administration of the drug is 60 per cent. The serum and intracellular half-life is 1.1 hour and 3 hours, respectively. The drug is metabolised to ZDV glucuronide, which is excreted in urine. ZDV delays onset of opportunistic infections and prolongs survival in persons with advanced HIV infection (Fischl *et al*., 1987). An increase in CD4 cell count and decline in plasma virus titre is seen within 4–8 weeks after commencement of therapy. By 6 months, these parameters recover to baseline levels. Clinical improvement is also seen in patients with HIV-related psoriasis, nail lesions, and arthritis (Lewin *et al*., 1997).

Dosage Forms and Dosage

ZDV is available as 100 and 250 mg capsules, 300 mg tablets, and syrup containing 10 mg per mL. For infants less than 4 weeks old, the dose is 4 mg per kg body weight. Between 4 weeks and 13 years of age, 180 mg per m^2 of body surface area is recommended. Above 13 years of age, the dose is 300 mg twice daily. The drug can be administered along with food (Harries *et al*., 2004). Doses of 1,000 mg per day or more have been used in patients with AIDS-related dementia. ZDV is given in the dose of 250 mg four times a day as prophylaxis for high-risk exposure (Lewin *et al*., 1997). There are no food restrictions (Fact Sheet 401, 2006).

Storage Requirements

ZDV should be stored in amber-coloured glass jars and is light sensitive (Harries *et al*., 2004).

Side Effects

Due to haematological toxicity, the bone marrow may be suppressed, resulting in anaemia and neutropenia. This toxicity is more severe in those with advanced disease. In symptom-free HIV-infected persons, the risk of anaemia is only

about 2 per cent, after 18 months of continuous treatment. Mean corpuscular volume (MCV) is often elevated. ZDV can cause short-term decrease in platelet counts in patients with HIV-related thrombocytopenia (Lewin *et al*., 1997). The drug should not be co-administered with d4T (Fact Sheet 401, 2006).

There may be subjective complaints of gastrointestinal intolerance, headache, insomnia, and asthenia. Nausea and headache are frequent complaints in the first 6 months of treatment and they decrease with continued treatment. Myopathy, associated with elevated levels of creatine phosphokinase (CPK), may be seen with long-term (more than 1 year) use. This condition is reversible within 8 weeks of stopping treatment. Rare toxic effects include fatty liver, lactic acidosis, mood disturbances, and bluish pigmentation of nails and mucosa (Lewin *et al*., 1997).

Monitoring During Therapy

During treatment, complete blood count and liver function tests should be performed every month for the first 3 months and later, every 2 months. CPK levels should be monitored twice-monthly after 1 year of treatment or if symptoms of myopathy occur. The treatment should be stopped if aminotransferase levels increase rapidly or if progressive hepatomegaly occurs. ZDV should be cautiously used in first trimester of pregnancy (Lewin *et al*., 1997).

[B] DIDANOSINE OR DI DEOXY INOSINE (DDL)

Pharmacology

Didanosine exhibits ARV activity against both HIV-1 and HIV-2, including strains resistant to ZDV. It has synergistic action with ZDV. During treatment, there is likelihood of emergence of HIV strains with reduced sensitivity to ddI. It is beneficial as initial treatment in children and in adults previously treated with ZDV. As compared to ZDV, it does not significantly cross the blood-brain barrier and is therefore ineffective in patients with AIDS-related dementia. The bioavailability on oral administration of the drug is 40 per cent. The serum and intracellular half-life is 1.6 hour and 12 hours, respectively. Half the ingested dose is excreted in urine (Lewin *et al*., 1997).

Dosage Forms and Dosage

The drug is available as oral suspension or paediatric powder/water (10 mg/mL) and chewable tablets in the strengths of 25, 50, 100, 150, and 200 mg. Enteric-coated beadlets in capsules are also available in different strengths. These beadlets can be removed from the capsules and sprinkled on small amount of food before consumption (Harries *et al*., 2004). The chewable tablets contain sufficient antacid since ddI is rapidly destroyed on exposure to acid (Lewin *et al*., 1997).

The dose for infants less than 3 months old is 50 mg per m^2 of body surface area twice daily. Between 3 months and 13 years, 90 mg per m^2 twice daily (or 240 mg/m^2 once daily) is advised. For children older than 13 years or whose body weight is more than 60 kg, the dose is 200 mg twice daily or 400 mg once daily. The tablets should be taken on an *empty* stomach at least 30 minutes before, or 2 hours after eating (Harries *et al*., 2004). The drug should not be administered within 1 hour of indinavir (IDV) or 2 hours of RTV (Fact Sheet 401, 2006).

Storage Requirements

Paediatric oral suspension should be refrigerated and shaken well before use (Harries *et al*., 2004).

Drug Interactions

The drug should not be co-administered with d4T. The side effects include diarrhea, nausea, vomiting, pancreatitis, abdominal pain, and neuropathy (Fact Sheet 402, 2006). Antacids in ddI tablets can reduce the absorption of ketoconazole and dapsone. Therefore, these drugs should be taken with food, several hours after taking ddI. Oral administration of ganciclovir doubles the absorption of ddI, causing toxic effects. Conversely, ddI halves the serum levels of ganciclovir and can reduce the effectiveness of the latter against cytomegalovirus infection (Lewin *et al*., 1997).

Side Effects

As compared to ZDV, ddI is less toxic to bone marrow. A major side effect is dose-related, predominantly sensory, symmetric peripheral neuropathy, which is reversible within weeks of stopping treatment. Persons with previous history of peripheral neuropathy are at high risk of recurrence. Mild to fatal dose-related pancreatitis may occur particularly in patients with previous history of pancreatitis or with history of risk factors for developing pancreatitis (drugs, alcohol). The patients should be warned about early signs of pancreatitis and peripheral neuropathy. Xerostomia may occur in 10 per cent of cases. Other toxic effects include hepatitis, electrolyte disturbances and potentially fatal rhabdomyolysis (Lewin *et al*., 1997).

Monitoring During Therapy

During ddI therapy, it is essential to monitor peripheral nervous system and serum amylase levels. The dose must be reduced or the drug should be withdrawn if signs of peripheral neuropathy develop or if serum amylase level is more than twice normal (Lewin *et al*., 1997).

[C] ZALCITABINE OR DI DEOXY CYTIDINE (DDC)

The production of this drug has been terminated in the United States in 2006 (Fact Sheet 401, 2006).

Dosage Forms and Dosage

The drug is available as 0.375 and 0.75 mg tablets. The initial oral dose is 0.75 mg three times a day, taken on an *empty* stomach. If side effects occur, the treatment should be stopped and resumption in a dose of 0.375 mg three times a day should be considered (Lewin *et al*., 1997). The bioavailability on oral administration of the drug is 85 per cent. The serum and intracellular half-life is 1.2 and 3 hours, respectively. Almost 70 per cent of the ingested dose is excreted in urine.

Pharmacology

Antiviral activity is similar to that of ddI. The drug is also active against ZDV-resistant strains of HIV and has synergistic action with ZDV. Superior ARV response is seen when the drug is combined with ZDV or saquinavir. However, combination of ZDV and ddC does not retard emergence of ZDV resistance. A marginal decrease in CD4 cell counts is seen after 8–12 weeks of therapy. There is a dose-dependent reduction in levels of circulating p24 HIV antigen (Lewin *et al*., 1997).

Side Effects

The patient should be warned about early signs of peripheral neuropathy. After about 8 weeks of treatment, dose-dependent, symmetric sensory peripheral neuropathy may occur. This initially involves the lower limbs and is reversible on stopping treatment. With the first few weeks of therapy, dose-dependent macular rash may develop mostly on the trunk and extremities. Stomatitis, including mouth ulcers, and fever may accompany the rash. Pancreatitis is rare (Lewin *et al*., 1997).

Monitoring During Therapy

During ddC therapy, it is essential to monitor peripheral nervous system and serum amylase levels. The dose must be reduced or the drug should be withdrawn if signs of peripheral neuropathy develop or if serum amylase level is more than twice normal (Lewin *et al*., 1997).

[D] LAMIVUDINE (3TC)

Dosage Forms and Dosage

It is available as 150 mg tablets and oral solution containing 10 mg per mL. FDC of 300 mg ZDV and 150 mg 3TC is available. In neonates (less than 1

month old), the dose is 2 mg per kg body weight twice daily. In patients older than 30 days and below 60 kg weight, the dose is 4 mg per kg body weight twice daily. The maximum dose for those weighing more than 60 kg is 150 mg twice daily (Harries *et al*., 2004). In case of renal insufficiency, the dose should be reduced (Lewin *et al*., 1997). The drug can be administered along with food (Harries *et al*., 2004). There are no food restrictions (Fact Sheet 401, 2006).

Pharmacology

Bioavailability on oral administration is 86 per cent in adults and less in children. The serum half-life is 3–6 hours and intracellular half-life is 12 hours. Lamivudine is excreted unchanged in urine. 3TC is a NNRTI. The drug acts by terminating chain of reverse transcriptase and is a weak inhibitor of this HIV enzyme. Lamivudine is active against HIV-1 and ZDV-resistant strains. It has synergistic action with ZDV. Lamivudine-resistant strains remain sensitive to ZDV (Lewin *et al*., 1997).

Storage Requirements

The oral solution should be stored at room temperature (up to 25°C or 77°) and used within 1 month of opening (Harries *et al*., 2004).

Side Effects

In adults, 3TC is well tolerated (Harries *et al*., 2004). The side effects include nausea, vomiting, fatigue, and headache (Fact Sheet 401, 2006). Macrocytosis and neutropenia are the commonest haematological side effects if the drug is used in combination with ZDV. Hair loss is rare. In children, past history and history of risk factors for pancreatitis should be elicited and their parents/guardians should be warned about early signs of pancreatitis. Serum amylase levels should be monitored in children (Lewin *et al*., 1997). The drug should not be combined with abacavir (ABC) and TDF unless additional ARV drugs are used (Fact Sheet 401, 2006).

[E] STAVUDINE (D4T)

Pharmacology

Bioavailability on oral administration is 80 per cent. The serum half-life is 1 hour and intracellular half-life is 3–5 hours. Fifty per cent of the ingested dose is excreted in urine. Stavudine improves clinical and immunological parameters in HIV-infected persons with CD4 cell count less than 500 cells per μL, who had previously taken ZDV. Higher CSF levels are achieved as compared with ddl or ddC (Lewin *et al*., 1997). Stavudine can be combined with 3TC or ddI, but *not* with ZDV, due to antagonistic ARV action (Harries *et al*., 2004; Lewin *et al*., 1997).

Dosage Forms and Dosage

The drug is available as oral solution containing 1 mg per mL and as 15, 20, 30, or 40 mg capsules. For persons weighing more than 30 kg, the dose is 30 mg twice a day. The maximum dose (more than 60 kg) is 40 mg twice daily (Harries *et al*., 2004). The dosage should be reduced in persons with renal insufficiency (Lewin *et al*., 1997). The capsules may be opened and mixed with small amounts of food. There are no food restrictions during treatment (Fact Sheet 401, 2006).

Storage Requirements

The oral solution should be stored under refrigeration and shaken well before use. The capsules should be stored in glass bottles (Harries *et al*., 2004).

Side Effects

The drug should not be used with ZDV or ddI (Fact Sheet 401, 2006). The patient should be warned about early signs of peripheral neuropathy and those with a past history of this condition (particularly after taking ddI or ddC) have a high risk of recurrence. Peripheral neuropathy is reversible if treatment is stopped. Headache and nausea may occur and decrease with continued treatment. Though pancreatitis is rare, past history of pancreatitis, or risk factors for this condition (ganciclovir or pentamidine therapy) should be elicited. Anaemia and neutropenia are infrequent side effects (Lewin *et al*., 1997). Chills, fever, and diarrhea have also been reported (Fact Sheet 401, 2006).

Monitoring During Therapy

During d4T therapy, it is necessary to monitor the peripheral nervous system, complete blood count, liver function tests, and serum amylase levels. The dose must be reduced or the drug should be withdrawn if signs of peripheral neuropathy develop or if serum amylase level is more than twice normal (Lewin *et al*., 1997).

[F] ABACAVIR (ABC)

Dosage Forms and Dosage

The drug is available as oral solution (20 mg/mL) and 300 mg tablets. The dose is 8 mg per kg body weight for patients younger than 16 years or less than 37.5 kg. For those older than 16 years or weighing more than 37.5 kg, the dose is 300 mg twice daily. The drug may be administered along with food and there are no food restrictions. An FDC of *ZDV 300 mg + 3TC 150 mg + ABC 300 mg* is available as Trizavir. The maximum dose (those weighing more than 40 kg) of this FDC is one tablet twice daily. The tablet cannot be split and therefore, for children

weighing less than 30 kg, Trizavir cannot be dosed accurately. At present liquid preparations of Trizavir are not available (Harries *et al*., 2004).

Side Effects

Patients must be warned about possible hypersensitivity reaction, which occurs in about 8 per cent of patients (Fact Sheet 401, 2006). If hypersensitivity reaction occurs, ABC should be stopped permanently (Harries *et al*., 2004). ABC should not be co-administered with 3TC or TDF (Fact Sheet 401, 2006).

[G] EMTRICITABINE (FTC)

The adult dose of the drug is 200 mg once daily. There are no food restrictions. The side effects include headache, nausea, vomiting, and skin rash (Fact Sheet 401, 2006). A FDC of EFV, emtricitabine, and TDF disopril fumarate called Atripla has been approved for use in HIV-1 infected adults by the FDA (USA) in July 2006. Atripla is the first once-pill, once-a-day ARV product (FDA, 2006).

[H] "NUKES" UNDER DEVELOPMENT

ELVUCITABINE (ACH-126, 443, beta-L-Fd4c) is an once-daily drug, which has shown activity against HIV that is resistant to several other "nukes" and is also effective against HBV.

MIV-210 (FLG) has shown activity against HIV that is resistant to several other "nukes".

RACIVIR has shown activity against HIV and HBV in laboratory studies. The drug exhibited anti-HIV activity that lasted more than 2 weeks after the drug was stopped. Probably, racivir can be used as a once-daily drug (Fact Sheet 410, 2006).

APRICITABINE (AVX 754, formerly SPD 754) has shown good activity against 3TC-resistant HIV and seems well tolerated.

AMDOXOVIR (MPD) is in Phase II studies and ocular problems detected in early studies are under investigation.

DIOXOLANE THYMIDINE (DOT) is being studied in the University of Georgia, USA.

KP1461 induces lethal mutations in HIV (Fact Sheet 410, 2006).

APPENDIX 3

NON-NUCLEOSIDE RTIs (NNRTIs)

These drugs (also called "non-nukes"), actually bind to reverse transcriptase and prevent its functioning. All "non-nukes" interact with many other drugs and therefore, the physician should elicit the medication history before starting

treatment and advise the patient to seek advice before taking any medication. NOTE – The dose of each drug may vary if ARV drugs are combined.

[1] NEVIRAPINE (NVP)

Pharmacology

On oral administration, the bioavailability is 90 per cent. The serum half-life is 25–30 hours. NVP is metabolized by cytochrome P450. Almost 80 per cent of the ingested dose is excreted in urine as glucuronide, 5 per cent is excreted unchanged in urine, and 10 per cent is excreted in faeces. 12 months of triple drug therapy (NVP, ddI, and ZDV) causes significant decrease in viral load. Monotherapy or dual therapy with ZDV is associated with rapid development of drug resistance (Lewin *et al*., 1997).

Dosage Forms and Dosage

NVP is available as oral suspension containing 10 mg per mL and as 200 mg tablets. The drug can be given along with food and there are no food restrictions (Fact Sheet 401, 2006). Since initiation of full-dose therapy is associated with development of skin rash in up to 50 per cent of patients, incremental doses are given as mentioned in Table 3.

Storage Requirements

Oral suspension can be stored in room temperature (up to 25°C or 77°F); must be shaken well before use (Harries *et al*., 2004).

Side Effects and Interactions

Fever, headache, and nausea have been reported (Fact Sheet 401, 2006). Hepatitis may occur in 1 per cent of cases. Steven-Johnson syndrome is rare, but the risk is increased on ingestion of drugs containing clavulanic acid. The drug *induces* (stimulates) cytochrome P450 enzyme. Since rifampicin, rifabutin, antiepileptics, oral contraceptives, and other protease inhibitors *reduce* the plasma levels of NVP, these drugs should not be co-administered (Collier *et al*., 1996).

Table 3. Incremental dosage for nevirapine (Harries et al., 2004)

Age	First 2 weeks	Next 2 weeks	Thereafter
15–30 days	5 mg per kg once daily	120 mg per m^2 twice daily	200 mg per m^2 twice daily
30 days to 13 years	120 mg per m^2 once daily	120–200 mg per m^2 twice daily	
>13 years	200 mg once daily	200 mg twice daily	

Monitoring during Therapy

Liver enzymes should be monitored during NVP therapy since abnormal liver function tests are common (Lewin *et al*., 1997). Patients should be warned about skin rash. If mild or moderate rash occurs, the drug is withheld and dosing is restarted from the beginning of dose escalation. In case of severe rash, NVP is to be discontinued (Harries *et al*., 2004).

[2] –DELAVIRIDINE (DLV)

Pharmacology

On oral administration, the bioavailability is 85 per cent. The serum half-life is 5–8 hours. The drug is metabolized partially by cytochrome P450. Of the ingested dose 51 per cent is excreted in urine as metabolites, 5 per cent is excreted unchanged in urine, and 44 per cent in faeces (Lewin *et al*., 1997).

Dosage Forms and Dosage

This drug is available as 100 mg tablets. The adult dose is 100–300 mg four times a day. Antacids and ddI should be avoided within 1 hour of administering the drug, but there are no food restrictions (Fact Sheet 401, 2006). Delaviridine (DLV) should be used only in combination with other ARV drugs. Triple drug therapy (DLV, ddI, ZDV) is used (Lewin *et al*., 1997).

Side Effects and Interactions

Diffuse maculopapular skin rash may develop in up to 30 per cent of patients. Mild headache, nausea, vomiting, diarrhea, and fatigue have been reported with its use (Fact Sheet 401, 2006). Liver enzymes may be elevated and hence, liver functions should be monitored (Lewin *et al*., 1997). DLV inhibits cytochrome P450 enzyme and interacts with multiple drugs. Drugs that decrease levels of DLV, thus increasing risk of therapeutic failure of DLV include phenobarbital, phenytoin sodium, rifabutin, and rifampicin. On the other hand, DLV increases blood levels causing potential toxicity of the following drugs if co-administered – clarithromycin, dapsone, ergot alkaloids, IDV, quinidine, saquinavir, and warfarin (Lewin *et al*., 1997). Terfenadine, astemizole, alprazolam, midazolam, and cisapride should also *not* be co-administered with DLV (Lewin *et al*., 1997).

[3] EFAVIRENZ (EFV)

This NNRTI is recommended only for children aged over 3 years. The drug is available as syrup containing 30 mg per mL and as capsules in the strengths of 50, 100, and 200 mg (Table 4).

Table 4. Dosage of efavirenz (Harries et al., 2004)

Weight of child (kg)	Capsule (liquid) dose*
10–15	200 mg (270 mg = 9 mL) once daily
15–20	250 mg (300 mg = 10 mL) once daily
20–25	300 mg (360 mg = 12 mL) once daily
25–33	350 mg (450 mg = 15 mL) once daily
33–40	400 mg (510 mg = 17 mL) once daily
>40	600 mg once daily

*The syrup requires higher doses than capsules.

EFV is best given at bedtime, especially in the first 2 weeks, to avoid side effects pertaining to the central nervous system. The drug can be co-administered with food, but high-fat meals increase absorption by 50 per cent. The capsules may be opened and added to food and the very peppery taste of the drug can be disguised by mixing with sweet foods or jam (Harries *et al.*, 2004). Side effects include vivid dreams, insomnia, anxiety, dizziness, skin rash, nausea, diarrhoea, and headache (Fact Sheet 401, 2006).

[4] "NON-NUKES" UNDER DEVELOPMENT

(+)-CALANOLIDE A is derived from a rainforest plant. It can easily cross the blood-brain barrier and remain the blood stream for a long time.

GW5634 (also known as 695634) is a precursor that is broken down in the body to produce GW 8248 that has better bioavailability. It can cause skin rash and elevate levels of liver enzymes.

MIV-150 has shown activity against HIV strains that are resistant to other "non-nukes" in laboratory studies (Fact Sheet 430, 2005).

ETRAVIRINE (TMC 125) and TMC 278 have exhibited activity against some HIV strains that are resistant to other "non-nukes".

BILR 355 BS is being developed against wild-type and NNRTI-resistant HIV.

CAPRAVIRINE (AG 1549, formerly S-1153) has shown disappointing results in a recent Phase II trial (Fact Sheet 430, 2005).

APPENDIX 4

PROTEASE INHIBITORS

These ARV agents target the HIV enzyme protease, which cleaves the *gag* polyprotein that is required for production of mature, infectious virions. PIs also inhibit viral assembly. Nausea and diarrhoea are common with PIs. Bulking agents, loperamide, and dietary modifications can be helpful for diarrhoea (Wig, 2002). All PIs interact with many other drugs and therefore, the physician should elicit the medication history before starting treatment and advise the

patient to seek advice before taking any medication. Drugs decreasing blood levels of PIs, causing their potential therapeutic failure include carbamazepine, NVP, phenobarbital, and rifampicin. PIs increase the blood levels of alprazolam, midazolam, triazolam, astemizole, terfenadine, cisapride, tricyclic antidepressants, felodepine, nifedipine, lovastatin, simvastatin, clarithromycin, cyclosporin A, and diazepam (Lewin *et al*., 1997).

[A] NELFINAVIR (NFV)

The drug is available as 250 mg tablets and as powder for oral suspension, to be mixed with liquid before administration. Each 5 mL level teaspoonful of the suspension contains 200 mg. The powder is faintly bitter; gritty and hard to dissolve. The drug is to be taken with meals or a snack (Fact Sheet 401, 2006). Administration along with acidic food or juice increases its bitter taste (Table 5).

The tablets can be halved, or crushed and added to food or dissolved in water. Because of difficulties in dissolving the powder, crushed tablets are preferred even for infants if appropriate dose can be given. Powder and tablets can be stored at room temperature (Harries *et al*., 2004). Side effects include nausea, diarrhoea, flatulence, abdominal pain, and weakness (Fact Sheet 401, 2006).

[B] INDINAVIR (IDV)

Pharmacology

This drug is indicated in HIV-infected adults. On oral administration, the bioavailability is 30 per cent. The serum half-life is 1.5–2 hours. IDV is effective when used alone and it exhibits synergistic ARV activity with ZDV, ddI, and NNRTIs. Undetectable viral loads have been achieved with triple therapy (IDV, ZDV, 3TC) in 88 per cent of patients (Lewin *et al*., 1997).

Dosage Forms and Dosage

IDV is available as 200 and 400 mg tablets and should be stored in cool, dry place. The recommended standard dose is 800 mg *every 8 hours* (not three times a day), to be taken 1 hour before or after meals, or with low-fat snack or with lots of water on empty stomach (Fact Sheet 401, 2006). Patients should be advised to avoid consuming grape fruit and its juice altogether when taking certain medicines

Table 5. Dosage of nelfinavir (Harries et al., 2004)

Age	Dose
<1 year	40–50 mg per kg body weight three times daily (or) 75 mg per kg twice daily
1–13 years	55–65 mg per kg body weight twice daily
>13 years	1,250 mg twice daily

such as IDV because the interacting effect may persist for up to 3 days after ingestion (ADRAC, 2003). IDV should be started in full standard dose if liver functions are normal. Dosage must be reduced in cases of liver impairment. Liver function tests should be monitored during IDV therapy (Lewin *et al*., 1997).

Side Effects

Patients should be advised to consume at least 1.5 L of fluid daily to reduce risk of nephrolithiasis, which may occur in 2–5 per cent of cases due to poor solubility of IDV in urine. Other toxic effects include headache, nausea, abdominal pain, skin rash, dry skin, pharyngitis, and alteration of taste. Dose-dependent hyperbilirubinemia and elevated levels of serum transaminases may occur and these decrease with reduction in dosage. Oesophageal reflux is seen in 3 per cent of cases. Since antacids prevent absorption of IDV, reflux should be treated with H_2 blockers and proton-pump inhibitors (Wig, 2002).

Drug Interactions

IDV, which is metabolised by cytochrome P450 isoenzyme CTP 3A4, interacts with drugs that *induce* or *inhibit* this enzyme. The drug should *not* be administered within 1 hour of ddI. Co-administration of the following drugs are to be avoided – astemizole, terfenadine, cisapride, triaxolam, midazolam, ergot alkaloids, and itraconazole. With ketoconazole treatment, the dose of IDV should be reduced to 600 mg three times a day. Use of rifampicin should be avoided for treatment of mycobacterial infections. If rifabutin is used, the standard dose of IDV should be halved (Lewin *et al*., 1997).

[C] RITONAVIR (RTV)

Pharmacology

RTV is metabolised by cytochrome P450 isoenzymes 3A4, 2D6, 2C9, and 2C10. Thus, it interacts with multiple drugs and a checklist (Table 6) should be used when any drug is being prescribed to patients on RTV therapy. Serum half-life is 3–5 hours (Lewin *et al*., 1997). When RTV is used in small doses to boost the action of other PIs, the name of the drug is suffixed with "/r". For example, SQV/r means saquinavir boosted with RTV.

Dosage Forms and Dosage

This drug is available as 100 mg capsules. It is indicated in HIV-infected patients older than 12 years of age. The recommended dosage is 600 mg twice a day, to be taken with meals. If gastrointestinal intolerance develops, the dosage should be halved and again increased to full dose within 3–4 days because subtherapeutic doses increase the risk of viral resistance (Lewin *et al*., 1997). The drug should be taken 2 hours apart from ddI (Fact Sheet 401, 2006).

Table 6. Checklist for drugs interacting with ritonavir (Lewin et al., 1997)

Group	Substrate
Analgesics, NSAIDS	Meperidine, piroxicam, propoxyphene
Antimicrobial agents	Clarithromycin, sulfamethoxazole
Anticoagulants	Warfarin
Antidepressants	Bupropion
Antihistaminics	Astemizole, terfenadine
Antimycobacterial drugs	Rifampicin, rifabutin
Antiretroviral drugs	Zidovudine, saquinavir
Barbiturates	Phenobarbital
Bronchodilators	Theophylline
Calcium blockers	Heptidil
Ergot alkaloids	Dehydro ergotamine
Gastrointestinal drugs	Cisapride
Neuroleptics	Phenytoin, Clozapine, pimozide
Opium derivatives	Codeine
Steroids	Dexamethasone, Ethinyl estradiol
Oral hypoglycemics	Tolbutaminde
Psychotropics	Chlorpromazine, alprazolam, estazolam, midazolam, triazolam, diazepam, flurazepam, clorazepate, zolpidem

Storage Requirements

RTV should be stored under refrigeration. But, single doses can be kept at room temperature (up to 25°C or 77°F) for 12 hours (Harries *et al*., 2004).

Side Effects

Toxic effects include nausea, headache, vomiting, and diarrhoea, which may decrease with time. Alteration in taste has been reported. Circumoral paresthesia (numbness and burning) is a dose-dependent side effect.

Monitoring during Therapy

Elevated levels of serum triglycerides (more than twice normal), uric acid, CPK, and hepatic enzymes may be seen. These parameters should be monitored and RTV should be stopped if hepatic enzyme levels are more than three times normal (Lewin *et al*., 1997).

[D] LOPINAVIR/RITONAVIR (LPV/R)

This combination is indicated in patients who are older than 6 months. LPV/r combination is available as oral solution (80 mg per mL LPV + 20 mg per mL RTV) and as capsules (133.3 mg LPV + 33.3 mg RTV). The oral solution has bitter taste. (Harries *et al*., 2004). Liquid preparations are to be taken with food while there are no food restrictions when capsules are used (Fact Sheet 401, 2006).

Dosage

For patients aged more than 6 months to 13 years: *Surface area-based dosing* – 225 mg per m^2 LPV + 57.5 mg per m^2 RTV twice daily. *Weight-based dosing*: 7–15 kg – 12 mg per kg LPV + 3 mg per kg RTV twice daily; 15–40 kg – 10 mg per kg LPV + 2–5 mg per kg RTV twice daily. The maximum dose for patients weighing more than 40 kg is 400 mg LPV + 100 mg RTV (three capsules or 5 mL oral solution) twice daily. Though the oral solution and capsules can be stored at room temperature (up to 25°C or 77°F) for 2 months, they should be preferably stored under refrigeration (Harries *et al*., 2004).

[E] SAQUINAVIR (SQV)

Pharmacology

SQV is indicated in HIV-infected patients older than 12 years of age. Low absorption may increase the risk of HIV-resistance to PIs. However, bioavailability is *improved* when SQV is taken with grapefruit juice or with RTV. Serum half-life is 1–2 hours. SQV is metabolised in the liver by cytochrome P450 isoenzyme 3A4. Low bioavailability (about 4 per cent) on oral administration is due to incomplete absorption and extensive first-pass metabolism (Lewin *et al*., 1997).

Additive or synergistic effects are seen when dual or triple combinations (with RTIs) are employed. Cross-resistance is not seen with RTIs but 20 per cent of SQV-resistant strains exhibit cross-resistance with other PIs. When combined with ZDV and ddC, saquinavir is highly effective in suppressing the viral load and in increasing CD4 cell counts, even in patients with relatively advanced disease (Collier *et al*., 1996). Saquinavir is available as 200 mg capsules. The recommended dosage is 600 mg twice a day, taken orally with, or within 2 hours of a high-fat meal (Lewin *et al*., 1997).

Drug Interactions

Drugs that induce hepatic enzymes (rifampicin, rifabutin, phenytoin, carbamazepine) further decrease bioavailability of saquinavir and should not be co-administered with saquinavir. Like other PIs, it interacts with many drugs. Rifampicin and rifabutin reduce the plasma levels of saquinavir by 80 and 40 per cent, respectively. Drugs that decrease levels of saquinavir, thus causing its therapeutic failure include rifabutin, rifampicin, carbamazepine, NVP, phenobarbital, and terfenadine. Saquinavir increases the blood levels of the following drugs, causing their toxicity if co-administered – alprazolam, astemizole, cimetidine, cisapride, clarithromycin, clindamycin, cyclosporin A, diazepam, felodepine, itraconazole, ketoconazole, lovastatin, midazolam, nifedipine, simvastatin, terfenadine, triazolam, and tricyclic antidepressants (Lewin *et al*., 1997). The herb St. John's Wort lowers the blood levels of some PIs and therefore should not be co-administered (Fact Sheet 449, 2006).

Side Effects

Triple therapy does not increase toxic effects (Fischl *et al*., 1987). Toxic effects include gastrointestinal intolerance, abdominal discomfort, nausea, diarrhoea, oral ulceration, skin rash, headache, and elevated transaminases. It should be used cautiously in patients with hepatic impairment (Lewin *et al*., 1997).

[F] OTHER PROTEASE INHIBITORS

TIPRANAVIR (Aptivus, PNU 140690) – This drug was approved by the US FDA in 2005 (Fact Sheet 449, 2006). Tipranavir boosted with RTV should not be used as part of an initial ARV regimen. The adult dose comprises two tablets (gel capsules) of 250 mg with one 100 mg tablet of RTV, to be taken with food, particularly high-fat meals, twice daily. The drug should be stored under refrigeration until the bottle is opened. After opening the bottle, the gel capsules may be stored for up to 60 days at room temperature. Its side effects include nausea, vomiting, diarrhoea, abdominal pain, fatigue, skin rash, headache, and aggravation of impaired liver function. Patients with hepatitis B or C should get their liver functions monitored periodically. Women taking oral contraceptives may get a skin rash and the efficacy of contraception may be reduced. The combination of tipranavir and RTV can cause increases in blood levels of cholesterol and triglycerides. The drug is best avoided in persons with bleeding disorders because few cases of internal bleeding were reported in 2006, some of them fatal. Tipranavir being a sulfa drug, history of sulfa allergy should be elicited before prescribing the drug. It interacts with multiple drugs (see under darunavir, below), lowers the blood levels of methadone, and causes excessive sedation if buprenorphine is co-administered (Fact Sheet 449, 2006).

Amprenavir (APV) – The drug may be used in combination with RTV. The adult dose of APV is eight tablets of 150 mg twice daily, to be taken with or without food. High-fat foods are to be *avoided*. The drug should not be taken within 1 hour of antacids. The reported side effects are nausea, vomiting, diarrhea, skin rash, circumoral paresthesia, and abdominal pain (Fact Sheet 401, 2006).

Atazanavir (ATV) – The adult dose is 200 mg once daily for patients new to ARV treatment or 150 mg with 100 mg of RTV once a day, to be taken with food. The adverse effects are bilirubinemia, nausea, vomiting, diarrhea, headache, skin rash, abdominal pain, tingling in hands or feet, depression, and cardiac arrhythmias (Fact Sheet 401, 2006).

Darunavir (TMC 114, Preztisa) – This drug was approved by the FDA (USA) in June 2006 (Fact Sheet 440, 2006) for use in HIV-infected persons who have already used other ARV drugs (Fact Sheet 450, 2006). The adult dose is 600 mg (two tablets of darunavir) along with 100 mg (one tablet) RTV, twice daily,

to be taken with food. The drug should be stored at room temperature. Its side effects are nausea, vomiting, diarrhea, and rhinorrhoea. Skin rash may be serious in rare cases. The combination of darunavir with RTV can increase blood levels of cholesterol and triglycerides. Since darunavir belongs to the sulfa group of drugs, history of allergy to sulfa drugs should be elicited from patients. Darunavir may interact with antitubercular drugs, antifungals, antiarrhythmics, several antihistaminics, sedatives, anticholesterol drugs, and drugs used for treatment of erectile dysfunction and migraine (Fact Sheet 450, 2006).

Fosamprenavir (FPV) – The adult dose is 700 mg twice daily (or) 700 mg twice daily with 100 mg RTV once daily (or) 700 mg once daily with 100 mg RTV twice daily. There are no food restrictions. The drug is reported to cause nausea, vomiting, diarrhoea, skin rash, circumoral paresthesia, and abdominal pain (Fact Sheet 401, 2006).

[G] PROTEASE INHIBITORS UNDER DEVELOPMENT

BRECANAVIR (GW640385, VX-385) has shown activity against wild strains of HIV and strains that are already resistant to current PIs. If used in a relatively low dose that would reduce side effects, it will be boosted with RTV. The side effects are mild to moderate; the most common is skin rash (Fact Sheet 440, 2006).

APPENDIX 5

ATTACHMENT AND FUSION INHIBITORS

Attachment inhibitors prevent HIV from attaching to the host cell. *Fusion inhibitors* block the ability of HIV to enter host cell by blocking the merging (fusion) of the virus with the host cell membrane. This prevents the HIV from entering and infecting human immune cells (NIAID, 2005). These drugs may prevent infection of a host cell by free virus in the blood stream or by contact with an infected cell. Most of these drugs are administered by injections or intravenous infusions because they are destroyed by the action of digestive acids (Fact Sheet 460, 2006).

Enfuvirtide (ENF, T-20)

The first fusion inhibitor enfuvirtide was approved for use as an ARV drug in the United States by the FDA in 2003. When HIV infects a human cell, it attaches itself to the cell and fuses with the cell membrane. Enfuvirtide stops this process of fusion and thus prevents infection of human cells by HIV. This drug has been studied in adults and children over 6 months of age. It is recommended only when the other ARV drugs are not effective. The drug does not exhibit

cross-resistance with any other ARV drug (Fact Sheet 461, 2006). It is expensive and requires parenteral administration. It is therefore, not suitable for use in situations with resource limitations (WHO, 2003a).

Dose – The adult dose is 90 mg per injection given subcutaneously, twice daily. For children, the dose is based on their body weight. The drug cannot be administered orally because it is destroyed by digestive acids (Fact Sheet 461, 2006).

Side Effects – Almost everyone develops skin reactions at the site of injection. These reactions may manifest as slight erythema, itching, swelling, pain, hardened skin, or hard lumps. Each reaction might last up to 1 week (Fact Sheet 461, 2006). Other side effects include headache, dyspnoea, pneumonia, chills and fever, skin rash, haematuria, vomiting, pain and numbness in feet or legs, dizziness, insomnia, and hypotension (Fact Sheets 401 & 461, 2006).

Drug Interactions – Enfuvirtide may increase the blood levels of tipranavir and RTV. There are very few known interactions with other ARV drugs. Enfuvirtide has not been studied for interactions with all drugs or dietary supplements. Health care personnel should elicit history of use of medications or dietary supplements from patients (Fact Sheet 461, 2006).

ATTACHMENT AND FUSION INHIBITORS UNDER DEVELOPMENT

AMD 070 blocks the CXCR4 receptor on CD4 T-lymphocytes to inhibit HIV fusion.

AK 602 is being developed by Kumamoto University, Japan and is in early human trials. It blocks the CCR5 receptor on CD4 T-lymphocytes to inhibit HIV fusion.

BMS-378806 is an attachment inhibitor that attaches to gp120 and prevents attachment of HIV.

MARAVIROC (MVC, UK-427–857) blocks the CCR5 receptor on CD4 cells to inhibit HIV fusion (Fact Sheet 461, 2006).

VICRIVIROC (SCH-417690, formerly called Schering-D) blocks the CCR5 receptor on CD4 cells. Phase III trials were discontinued due to poor virologic control in patients who had never received ARV treatment. The study is likely to be repeated at a higher dose of the drug (Fact Sheet 461, 2006).

TNA-355 is a genetically engineered monoclonal antibody that blocks the CD4 receptor. It may be administered by intravenous infusion or as a twice-monthly injection.

INCB 9471 is in Phase I trials in healthy volunteers.

PRO 140 and PRO 542 block fusion by binding to a receptor protein on the surface of CD4 cells.

SIFURVITIDE is being developed in China and human trials are to begin soon (Fact Sheet 461, 2006).

APPENDIX 6

MISCELLANEOUS DRUGS

NUCLEOTIDE ANALOGUE RTI (NTRTI)

TENOFOVIR or tenofovir disoproxil fumarate (TDF) – The adult dose is 300 mg orally, once daily. There are no food restrictions, but the drug is to be taken 2 hours before, or 1 hour after ddI. The side effects are usually mild and include nausea, vomiting, and loss of appetite. The drug should not be co-administered with 3TC and ABC unless additional ARV drugs are included in the regimen (Fact Sheet 401, 2006). The dose of the drug may vary if ARV drugs are combined. TDF, with or without emtricitabine, reduces infection rate in high-risk groups but its prophylactic use may accelerate emergence of drug resistance. TDF has reportedly been misused as a "party" pill by uninfected individuals who planned to engage in high-risk activity (Sepkowitz, 2006). The prevalence of resistance to TDF has increased from about 5 per cent before 1996 to at least 15 per cent between 1996 and 2003 (Masquelier *et al*., 2005).

INTEGRASE INHIBITORS

Once the reverse transcriptase enzyme changes the HIV's genetic code from a single strand to a double strand, the double strand gets inserted into the genetic code of the host cell with the help of integrase enzyme. Integrase inhibitors block the action of integrase enzyme. *Gilead 9137* (JTK-303), discovered by Japan Tobacco and now licensed to Gilead Sciences, has shown promising results in early studies. *MK-0518* is moving to advanced stage of human trials (Fact Sheets 402 & 470, 2006).

ANTISENSE DRUGS

These are "mirror images" of part of the genetic code of HIV that lock on to the virus to prevent it from functioning. *HGTV43* an "antisense" therapy that aims to produce CD4 T-lymphocytes that resist infection by HIV. *VRX496* is another "antisense" drug. Both are under trial (Fact Sheets 470 & 480, 2006).

HYDROXYUREA

Hydroxyurea does not act on HIV directly, but enhances the action of ddI and d4T. When taken in the dose of 300 mg twice daily, hydoxyurea showed the best results in terms of tolerability and reduction of viral load. Since the drug blocks an enzyme produced by human cells, HIV cannot develop resistance to it. Hydroxyurea can slow down mutations in HIV so that it takes much longer for resistance to develop to other ARV drugs. It has been approved as an antimalignancy drug by the FDA (USA), but not as an ARV drug. Hydroxyurea is also

effective in sickle cell anemia. The most serious side effect of hydroxyurea is pancreatitis that caused some deaths. Other side effects include nausea, vomiting, diarrhoea, weight gain, hair loss, peripheral neuropathy, and changes in skin colour. Since the drug can damage the bone marrow causing anaemia and neutropenia, hydroxyurea should not be co-administered with ZDV because both drugs can damage the bone marrow. Hydroxyurea can increase the side effects of ddI, cause serious birth defects, and reduce gains in CD4 cell counts (Fact Sheet 479, 2006).

MATURATION INHIBITORS

This group of drugs prevents maturation of internal structures in new virions. *BEVIRIMAT* (PA457), the first maturation inhibitor, has shown ARV activity and will probably be a once-a-day drug (Fact Sheet 470, 2006).

ZINC FINGER INHIBITORS (OR ZINC EJECTORS)

The inner core of HIV (the nucleocapsid) is held together by structures called "zinc fingers". Zinc finger inhibitors (or zinc ejectors) are drugs that can break apart these structures and prevent HIV from functioning. Since it is believed that the nucleocapsid core cannot mutate very easily, a drug that works against the zinc fingers might be effective for a long time. However, zinc fingers are not exclusive to HIV and zinc finger inhibitors could have serious side effects. *AZODICARBONAMIDE* (ADA) has been tested but there are no recent reports on its development (Fact Sheet 470, 2006).

MICROBICIDES

Technically microbicides are not intended to be used as part of ARV treatment. Microbicides are anti-HIV substances that could reduce the risk of HIV infection during vaginal or anal intercourse. Ideally, microbicides should be used in addition to condoms. Currently, the only available effective tools for HIV prevention are male and female condoms that need cooperation of the male partner. But in situations where male partners object to use of condoms, microbicides could reduce the risk of HIV transmission. Use of these products can be controlled by women without the need for cooperation from the male partner. Women might be able to use some products without their partners' knowledge. It is estimated that microbicides have the potential to prevent about 2.5 million HIV infections within 3 years, if they worked only 60 per cent of the time and used by only 20 per cent of women in 73 low-income countries. In addition, microbicides may prevent some other STIs besides HIV. However, success of microbicides depends on people remembering to use them correctly and consistently during each act of coitus. Microbicides can be incorporated in gels, foams, creams, thin films, or vaginal pessaries. The possible mechanisms of

action include immobilising the virus, creating a barrier between the virus and epithelial cells, and preventing HIV from reproducing and establishing infection after it has entered the body. So far, no anti-HIV microbicide has been approved. Microbicides closest to approval are Carraguard, cellulose sulphate gel (also being studied as a contraceptive), PRO 2000 Gel, BufferGel, and Savvy (Fact Sheet 157, 2006).

IMMUNE THERAPIES IN DEVELOPMENT

Concept of Immune Restoration

"Immune restoration" is repairing the damage done to the immune system. A healthy immune system has a full range of CD4 T-lymphocytes that can fight different pathogens, including opportunistic organisms. The first CD4 cells that HIV attacks are the ones that specifically fight HIV. It is believed that increases in CD4 cell counts after ARV therapy is indicative of immune restoration. But, the new CD4 cells are probably copies of the existing types of CD4 cells. If some types of CD4 cells were lost, they do not reappear immediately. This could leave some gaps in the body's immune defences. Immune restoration explores ways to fill these gaps (Fact Sheet 481, 2006).

When HIV enters the blood stream through any one of the routes of transmission, it is attracted by lymphocytes that have matured in thymus and bear CD4 receptors on their surface. It was believed that the thymus shrinks and stops maturation of lymphocytes to CD4 cells by the age of 20 years. Recent research reveals that thymus continues working, may be up to the age of 50 years. If the viral load is under control for a few years as a result of effective ARV therapy, the thymus might make new CD4 cells that could fill these gaps and restore the immune system. Older persons with HIV infection might need hormonal stimulation of thymus or thymus transplantation (Fact Sheet 481, 2006).

Approaches for Immune Restoration

Cell Expansion: The non-infected cells from the HIV-infected patient are multiplied in vitro and then infused back into the body (Fact Sheet 481, 2006).

Cell Transfer: Transfusing immune cells from patient's HIV-negative twin or relative (Fact Sheet 481, 2006).

Cytokines: Cytokines are the body's chemical messengers that support the immune response (Fact Sheet 481, 2006). Some immunomodulators use cytokines to increase the strength of the immune response to HIV (Fact Sheet 402, 2006). Cytokines under trials include – Ampligen, a form of interferon; Interleukin-2 (IL-2, Aldesleukin, Proleukin); Multikine, a mixture of several cytokines; and Bay 50–4798, a modified recombinant form of IL-2. Interleukin-7 is being developed as a general immune system booster. Tumour necrosis factor-alpha is an immune

system protein that is overproduced in immune disorders. A TNF-alpha blocker (that blocks this protein) is under trial (Fact Sheet 480, 2006).

Gene Therapy: Gene therapy attempts to make the bone marrow cells immune to HIV infection. These genetically changed cells would then travel to the thymus and mature to form CD4 cells (Fact Sheet 481, 2006). Gene therapies under study include – M 870 that makes T-lymphocytes resist infection by HIV; genetically modified CD4 and CD8 cells that block attachment of HIV; RRz2, a ribozyme that attacks *tat* gene of HIV; and VRX 496, a genetic factor that infects T-lymphocytes and attacks genetic code of HIV (Fact Sheet 480, 2006). Also being studied are Mifepristone (VGX410, RU486) that interferes with the viral protein vpr; and BI-201, an antibody designed to block HIV's *tat* gene (Fact Sheet 470, 2006).

Immunotherapy: HRG 214, a genetically engineered group of antibodies to HIV, is being studied for use as a passive immunotherapeutic agent. Dermavir, a novel immunotherapeutic agent that can be applied to the skin, is under study (Fact Sheet 481, 2006).

Other Immune Modulators: Immunitin (HE 2000), an immune regulating hormone has showed promising results in strengthening the humoral immune response. AVR 118 has showed promising results against AIDS-related wasting and anorexia. TH 9507, a growth hormone inducer, is being studied for treatment of visceral fat accumulation in lipodystrophy. Murabitide, that uses fragments of bacteria to stimulate the overall immune response, is being studied by Dr. Georges Bahr in France. Reservatrol is a chemical found in several plants and skin of red grapes. It protects plants against pathogens. It is being studied for immune boosting properties in HIV-infected persons. Reticulase, a nucleic acid, has shown increases in CD4 and CD8 cell counts, fewer opportunistic infections and weight gain in placebo-controlled studies. No toxic side effects have been reported so far. Reticulase is administered by subcutaneous injection. Zenapax (Dachzumab, anti-CD25) is being studied by National Institutes of Health, USA to reduce the viral load beyond what ARV therapy can achieve (Fact Sheet 480, 2006).

Dehydroepiandrosterone (DHEA): This is the steroid hormone produced by the adrenal glands. DHEA can be transformed in the body to testosterone, oestrogen, or other steroids. In normal adults, levels of the hormone decrease steadily after peaking at the age of about 20 years. HIV patients with lipodystrophy have very low levels of DHEA. A clinical trial is studying the effects of DHEA supplementation in HIV-infected individuals (Fact Sheet 724, 2006). Technically DHEA is not part of ARV treatment.