

Chapter 11

Pharmacology**Overview**

Drug therapy for persons living with HIV/AIDS is often complex and requires careful individualisation of drug choice, doses, and frequencies.

Reasons for this include:

- Altered absorption owing to opportunistic infections (OIs) that can themselves affect absorption or cause severe diarrhoea or ulceration.
- Dehydration and compromised renal function due to symptoms such as diarrhoea, sore mouth, and swallowing difficulties.
- Deteriorating renal function at end of life.
- Compromised hepatic function from a number of antiretroviral drugs (ARVs) and drugs used for opportunistic infections (OIs).
- Potential interactions among multiple drugs, altering therapeutic levels or severity of toxicities.
- Compromised hepatic function due to herbal and traditional medicines.

This chapter outlines the pharmacological issues to consider in giving medicines to patients with HIV/AIDS receiving palliative care, including potential interactions and issues relating to specific patient groups. The first section outlines the clinical relevance of general pharmacological principles. The second section then focuses on the relevant clinical pharmacology of ARVs, using the South African ART 'roll-out' as a case example. Appendix 2 at the end of the Guide provides a proposed 'essential medicines' list and guidance on the effect of hepatic, renal impairment, use in pregnancy, breastfeeding, and formulation for these drugs. Appendix 3 lists drug interactions. Chapter 12: Integration of Palliative Care with ART provides further discussion of the clinical issues of providing ART.

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At a Glance

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Pharmacologic Principles Relevant to Symptom Management

Application of basic pharmacological principles is important to ensure that drugs are used in appropriate doses and adverse effects minimised. Persons living with HIV/AIDS who receive palliative care require careful individualisation of their medication, but even in resource-limited settings good symptom control and appropriate use of ART with few adverse effects can be achieved.

Adverse Drug Reactions

All medicines, including traditional and herbal medicines, will have some unwanted effects in some patients. It is important to be familiar with:

- The potential adverse effects of the drugs you use
- Whether the drug should be stopped or dose reduced, or if it is preferable to simply monitor the patient regularly and continue in the same dose, if an adverse effect occurs
- How potential or actual adverse reactions can be minimised

In each case the impact on the patient's quality of life needs to be central in the decision.

If an adverse effect occurs, ensure a full drug history is taken including herbal and traditional remedies. To assess whether a drug is the cause, relate the occurrence to when each drug and treatment intervention was started or stopped. Remember, dose-related adverse effects can be exacerbated by impairment of hepatic and renal function or by increased blood levels of a drug following commencement of an interacting drug.

Herbal and Traditional Medicines

HIV patients often have other sources of medicines besides medical doctors. The same pharmacological principles apply to herbal and traditional medicines as to Western medicines. Some Western medicines are derived from plants from which the active ingredient(s) is purified and quantified. The amount of the active component(s) in traditional and herbal medicines is not so precise, and they may also contain other active substances. In addition, side effects and drug interactions are less well documented.

- Always ask your patients if they are taking any other treatment(s) including traditional and herbal medicines.
- Remember that herbal and traditional medicines can:
 - Cause adverse reactions
 - Accumulate with organ failure
 - Interact with other drugs, increasing or decreasing the effectiveness of the other drug(s) or themselves

Note: If you suspect that a drug may have caused an adverse reaction, altered the efficacy or toxicity of another drug, or accumulated following organ failure it is good practice to document this (see Chapter 36: Drug Policy). This is particularly important for herbal and traditional medicines, where documented information and studies are limited.

Pharmacokinetics

Pharmacokinetics describes the way drugs are:

- Absorbed
- Distributed within the body
- Metabolised (broken down) in the body
- Excreted

These are inter-linked processes, which influence the effect of a drug at any one time in a particular patient.

Pharmacokinetics: Absorption

Drug Formulation

Most drugs are absorbed into the systemic circulation, where they are transported to their site of action. Absorption depends on drug formulation.

Oral Preparations

Oral preparations require absorption across the gastro-intestinal tract. This depends on:

- Concentration of non-ionised to ionised drug (affected by pH)
- Drug's lipid solubility
- Gastric emptying time (reduced by metoclopramide, domperidone)
- Rate of dissolution of tablet (Some preparations are designed to have steady slow absorption — these tablets/capsules can not usually be crushed, chewed nor opened.)

Usually only a portion of the drug is absorbed.

Injectable Preparations

Intravenous and subcutaneous injections are absorbed quickly.

Intramuscular absorption is much slower and more erratic, especially when drugs are suspended in oily solutions.

Circulation at the site of absorption affects these routes:

- Increased blood flow occurs with massage, local application of heat.
- Decreased blood flow is seen with lymphoedema, vasoconstrictor agents, shock.

Topical Preparations

- Few drugs readily penetrate intact skin. Absorption is proportional to lipid solubility. Absorption through abraded or damaged skin can occur readily.
- Inflammation can increase cutaneous blood flow which increases absorption.
- Occlusive dressings increase absorption.
- Increased temperature: ↑ absorption

Examples of Relevance to Clinical Practice

- As many oral drugs are not completely absorbed (and/or are partially inactivated by the liver before they reach the systemic circulation) the amount of oral drug required is often greater than that required by injection to achieve the same therapeutic level. For example, the equivalent therapeutic dose of oral morphine to subcutaneous morphine is 3:1.
- Itraconazole has poor bioavailability. Its absorption is increased in an acid environment (e.g., if taken with cola drinks) and decreased when taken concurrently with antacids.
- Nystatin suspension (used for oesophageal candidiasis) is not absorbed through the gastro-intestinal tract but works very effectively through local action. (Nystatin would be too toxic to use if it were absorbed). Fluconazole is also used to treat oesophageal candidiasis, but is absorbed. In severe hepatic impairment fluconazole metabolism is reduced and the drug can accumulate, causing toxicity. Nystatin however can be used safely in hepatic impairment as it is not absorbed.
- Ritonavir inhibits both cytochrome P450 and p-glycoprotein, which are involved in absorption of drugs in the gastro-intestinal tract. Inhibition of cytochrome P450 and p-glycoprotein results in enhanced bioavailability of other drugs, for example lopinavir in the co-formulation of lopinavir and ritonavir.

Drug Interactions Affecting Absorption

Both the extent and/or rate of absorption can be altered by drug interactions. For example, calcium (in milk) can decrease the absorption of ciprofloxacin and tetracycline. This can be avoided by advising the patient to not drink milk an hour before and an hour after taking the tablets.

- Delayed absorption is not normally clinically important (exceptions include 'as required' analgesia).
- Decreased absorption can lead to ineffective therapy.

Pharmacokinetics: Distribution

How long a medicine takes to begin to exert its effect on the patient depends on the rate of absorption and rate of distribution from the circulation to the site where it has an action. The drug will also be distributed from the circulation to other tissues and organs. This is a reversible process. Highly perfused organs receive most of the drug in the first few minutes following absorption. In others, such as muscle, skin, viscera, and fat, it may be several minutes or hours before equilibration is achieved. Reservoirs can occur from which the drug slowly diffuses back into the circulation. This can lead to accumulation of drugs given regularly, causing prolonged action.

- Highly fat-soluble drugs are affected by malnutrition and obesity.
- Care is needed in patients with ascites or pleural effusions.

Drug Interactions Related to Distribution

Most drugs loosely bind to plasma proteins; the degree of protein binding depends on the drug. Only unbound drug is available to interact with receptors and exert an effect. One drug may displace another from plasma protein binding sites but this is usually not clinically important, as increased elimination of the free drug then occurs to restore the equilibrium.

Pharmacokinetics: Metabolism

First Pass Metabolism

Following absorption, oral preparations circulate to the liver by the portal vein. Here some drugs are metabolised. This may mean:

- Prodrug (inactive form of drug) → active drug
- Active drug → inactive
- Active drug → toxic metabolites

In patients with severe hepatocellular impairment this 'first pass metabolism' is decreased. This could mean a drug has:

- Reduced effect (↓ conversion from prodrug to active drug)
- Increased effect (↓ inactivation)
- Decreased toxicity (↓ conversion to toxic metabolites).

Note: Injections as well as rectal and sublingual administration avoid first pass metabolism. This increases the bioavailability of some drugs when given in these forms rather than orally.

Pharmacokinetics: Hepatic Excretion

Hepatic Metabolism

Both oral drugs and those that reach the systemic circulation from other routes pass through the liver, where many are metabolised to:

- Inactive compounds which are then excreted (e.g., paracetamol)
- Active compounds which exert a therapeutic effect before being excreted. These may be further metabolised before being excreted (e.g., codeine → morphine).
- Toxic metabolites (e.g. pethidine → norpethidine —accumulation can cause convulsions)

The major group of enzymes involved in hepatic metabolism are the cytochrome P450 mixed-function oxidase group of enzymes. They work through both oxidation and reduction.

Drug Interactions Related to Metabolism

Some drugs inhibit or slow down these enzymes whilst some 'induce' or increase the activity of the enzymes (see Box 11.1)

Box 11.1:

Enzyme Inhibitors and Inducers

Inhibitors include: **Inducers include:**

Cimetidine	Carbamazepine
Ciprofloxacin	Corticosteroids
Erythromycin	Isoniazid
Fluconazole	Cigarette smoke
Itraconazole	Phenytoin
Indinavir	Rifampicin
Quinine	
Ritonavir	

Enzyme Inhibition

Inhibition of the P450 system occurs a few hours following administration of an 'inhibitor' drug. Inhibition results in an increased concentration of any other drugs metabolised by the P450 system. This can lead to an increase in that drug's activity or toxicity, or for pro-drugs a decrease in their activity.

- Cimetidine reduces diazepam metabolism leading to increased effect of diazepam (e.g., ↑ sedation).
- Ciprofloxacin reduces theophylline metabolism leading to increased effect and possible toxicity of theophylline.
- Quinidine inhibits the biotransformation of codeine to morphine (↓ effect).

Enzyme Induction

Enzyme induction has a gradual onset and decrease, as it depends on the synthesis or breakdown of new enzymes. Drugs that induce P450 cause a decrease in the plasma concentration of drugs that are metabolised by P450 or an increase in active metabolites of pro-drugs.

- Rifampicin increases phenytoin clearance.

Note: Non-nucleoside anti-retrovirals and protease inhibitors are extensively and exclusively metabolised by cytochrome P450 enzymes. Co-administration of enzyme inducers causes risk of subtherapeutic levels and risk of developing resistance.

Co-administration of enzyme inhibitors can lead to toxicity from the PIs and NNRTIs.

Ritonavir is the most potent enzyme inhibitor known.

Hepatic Disease and Drug Handling

The liver has a large tissue reserve, therefore altered drug handling is not usually clinically significant except in severe disease. Liver function tests are a poor predictor of an individual's capacity to metabolise drugs.

- Care should be taken in patients with jaundice, ascites, or evidence of hepatic encephalopathy.
- Care should be taken with drugs with narrow therapeutic index (e.g. phenytoin) or large 1st pass metabolism
- Note: A significant proportion of patients with HIV/AIDS in sub-Saharan Africa have hepatitis co-infection. Use of potentially hepatotoxic drugs in these patients leads to a higher risk of severe and potentially fatal hepatic adverse events (see Box 11.2).

Box 11.2:**Hepatic Disease and Drug Handling****Cirrhosis causes:**

- Reduced clotting factors: Care must be taken with drugs which impair haemostasis or predispose to bleeding (e.g., NSAIDs, salicylic acid).
- Increased portal tension: Leads to increased risk of varices.
- Increased Na and water retention: This is exacerbated by NSAIDs, corticosteroids.

Note: Care should be taken with opioid analgesics and propranolol.

Chronic hepatitis causes:

- Reduced clotting factors: Care should be taken with drugs which impair haemostasis or predispose to bleeding (e.g., NSAIDs, salicylic acid).

Hepatic encephalopathy causes:

- Increased sensitivity to sedative effects so care should be taken with opioids, benzodiazepines, chlorpromazine, barbiturates.

Note: The following can precipitate encephalopathy in severe hepatic impairment: sedative drugs, opioid analgesics, diuretics that can cause hypokalaemia, and drugs which cause constipation.

Intra-hepatic or extra-hepatic obstructive jaundice can be caused when drugs that are excreted unchanged in the bile accumulate (e.g., rifampicin).

Hepatotoxicity: In severe hepatic disease drugs causing dose-related hepatotoxicity may do so at lower doses and those associated with idiosyncratic hepatotoxicity do so with a higher frequency.

Age: Elderly people generally have an age-related decrease in liver mass, hepatic enzyme activity, and hepatic blood flow. This is important for drugs with a high hepatic extraction ratio (e.g., amitriptyline).

Pharmacokinetics: Renal Excretion

Many drugs and their metabolites are excreted through the kidneys.

Drug Interactions Related to Excretion

Excretion occurs by three processes:

Glomerular Filtration

- Depends on plasma protein binding and glomerular filtration rate.
- A drug which is displaced from protein binding sites by another drug initially has a higher unbound, 'active' concentration. However, this is not normally clinically significant as this increased 'unbound' drug will be able to pass into the tubules and hence have increased secretion. Unless there is renal impairment, equilibrium is re-established quickly.

Active Tubular Secretion

- Bidirectional: secretion or re-absorption
- Non-selective; similar organic ions compete for transport. For example:
 - penicillin and probenecid → increased penicillin levels
 - methotrexate and aspirin / NSAIDs → increased methotrexate levels.

Passive Tubular Re-absorption

- Occurs in the proximal and distal tubules
- pH dependent; when tubular urine is more alkaline, weak acids are excreted more rapidly. For example:
 - Sodium bicarbonate is used to increase methotrexate (an acid) excretion and prevent toxicity.

Adverse Drug Reactions Related to Renal Impairment

Drugs and active metabolites that are excreted unchanged by the kidney will accumulate in renal impairment. Renal impairment is not important for drugs that are metabolised to inactive compounds by the liver.

Drugs are sensitive to all degrees of renal impairment.

Care should be taken with drugs excreted unchanged or that have active metabolites excreted by the kidney (e.g., digoxin, tetracyclines).

Renal and Hepatic Function Tests

In the majority of situations in which persons with HIV/AIDS are receiving palliative care, routine testing of renal and hepatic function would be inappropriate. In addition, in many health care settings in SSA facilities are not available for routine renal and hepatic function testing. It is more important that health care workers are aware of:

- Drugs which may cause renal or hepatic impairment
- Clinical signs of renal and hepatic impairment
- The increased risk of renal or hepatic impairment in HIV disease

Regularly assess patients clinically and consider the possibility of organ impairment if adverse effects occur.

Appendix 2 provides guidance on drug choice, dose, and frequency which should be considered in patients with renal or hepatic impairment. Although creatinine clearance is suggested as a guide to the degree of impairment, clinical symptoms and judgement should be used rather than blood tests in the majority of cases. In each case consider the risks and benefits of using each drug and of under- or over-dosing. Dose reductions, increasing frequency, or stopping the drug are more important when:

- Drugs have a narrow therapeutic index.
- Serious toxicities occur in higher doses.
- A suitable alternative is available.
- The drug is used to palliate mild symptoms.

If the patient does have organ impairment you will not be under-dosing by reducing the dose appropriately as the drug will simply be cleared more slowly.

Paediatric Medicine

Many of the drugs commonly used for children are only licensed for adults (usually >12 years of age). In practice, data is often extrapolated from adults to children. There need to be a number of precautions in this:

- Some drugs are handled differently by children; the liver and kidneys develop at different rates.
- Premature babies and those <1 month absorb and excrete drugs differently than older infants, so extra care is required.
- Young children have immature immune systems and therefore may be less effective at fighting infections than adults.
- There is often little or no research or post-marketing data on the tolerability and toxicity of combinations of drugs used in children.

'Off label' use of licensed drugs also occurs through modification of adult preparations to make them more suitable for children (see the formulation).

HCWs and carers need to be extra careful and monitor continually for unwanted effects.

HCWs prescribing drugs 'off label' are responsible for any untoward effects or events.

Pregnancy and Breastfeeding

Some drugs and metabolites are able to cross the placenta and some are excreted into breast milk. The cost-benefit for both mother and foetus/neonate need to be considered carefully in each individual case. Discuss fully with the mother the benefits, possible adverse effects, and alternatives. Appendix 2 gives guidance as to potential harm each drug may cause if used in pregnancy or whilst breastfeeding. The Web site www.perinatology.com also provides detail on individual drugs. Appendix 2 includes some manufacturers' recommendations which may be more applicable in countries where alternative drugs, clean water, and affordable formula milk are available.

Measures to prevent vertical transmission of HIV should be taken. Of the estimated 700,000 children worldwide who were infected with HIV in 2003, almost all cases resulted from vertical transmission or breastfeeding (WHO, 2004). However, unless mothers can be guaranteed clean water and can afford formula milk, the risk of serious waterborne infections and the benefits of breast milk outweigh the potential risk of HIV transmission from breast milk. Heat-treating expressed breast milk will kill any HIV virus in the breast milk. However, this also reduces levels of other immunoglobulins, is likely to be impracticable time wise, requires a clean water source, and ideally requires sterilisation of containers. As breastfeeding is not recommended where clean water is available and formula affordable, manufacturers have not studied the risks to infants, making clinical data very limited. For this reason, advice on risks whilst breastfeeding is omitted from the table of ARVs in Appendix 2.

Because of the advantages of breastfeeding, it is usually preferable for a mother to continue breastfeeding if a drug secreted into breast milk is required and there is no alternative drug available (WHO / UNICEF, 2003). The mother should be educated regarding possible adverse effects, the need to refer back to clinic if any occur, and the importance of stopping breastfeeding until treatment is complete if adverse effects are seen. Teach the mother to express her milk to maintain the supply so that she can resume breastfeeding after the course of treatment. The exceptions, when breastfeeding should be stopped entirely, include all cancer chemotherapy drugs and radioactive substances.

Route of Administration

Oral Administration

The oral route is almost always the preferred administration route in palliative care.

Advantages:

- Maintains dignity
- Allows patient control
- Reduces infection risk compared to injections
- Is cost effective
- Reduces incidence of side effects compared to injections as it produces a lower peak concentration
- The drug can be stopped easily if adverse effects occur.

Many palliative care patients and paediatric patients have difficulty swallowing tablets and capsules and require liquids or crushed tablets. Data on how these can affect both the efficacy and toxicity of drugs is limited.

Some general principles can be applied:

1. Slow-release or modified-release preparations have a special coating designed to release the drug slowly. Crushing will result in a higher peak concentration (potentially toxic) and a shorter duration of action (producing a sub-therapeutic state for a period) than is intended.

Slow-release and modified-release preparations should not be crushed nor made into suspensions/syrups.

2. Enteric coated tablets are designed to prevent drug dissolution in the stomach and to promote absorption in the small intestine. Crushing enteric coated tablets can cause stomach irritation or decrease drug effectiveness.

3. Stability data (physical, chemical, and microbiological) for extemporaneously prepared products is very limited. It is unlikely quality control of the product and ingredients will be carried out.

Give extemporaneous products the shortest practical expiry.

4. Take extra care to minimise exposure when crushing drugs which have a high incidence of allergic reactions e.g. antibiotics, chlorpromazine

5. Crush tablets between two metal spoons; avoid plastic as some drugs adhere to plastic.

6. Do not use boiling or hot water to dissolve tablets as it may affect their bioavailability.

7. Hard gelatine capsules can often be opened and the powder mixed with a small amount of sterile water. With soft gelatine capsules, withdraw the contents using a needle and syringe, but note some may adhere to the gelatine leading to lower than anticipated levels.

8. If diluting commercial liquids stability may also be reduced as any preservative will be diluted.

Appendix 2 contains information regarding whether or not tablets are likely to disperse or can be given by another route. This information is based on practical experience and anecdotal information. Health care workers must be aware that administering drugs in another form will be 'off license' and thus they must be prepared to accept responsibility for any adverse effects and decreased efficacy.

In a few cases the oral route may not be the most suitable and an alternative route is preferable. For example, patients with:

- Severe oral pain or pain on swallowing
- Dysphagia
- Odynophagia
- Obstruction
- Uncontrollable vomiting
- Diminishing conscious level

If available, buccal, sublingual, and rectal preparations can be useful for patients unable to swallow. Absorption is rapid via these routes and avoids first pass metabolism. Buccal and sublingual preparations may not be suitable if the patient has an impaired mental state, dry mouth, or excessive salivation.

Within palliative care the use of some oral preparations rectally is recognised (e.g., morphine slow release tablets — but this is an ‘off-label’ use). Rectal preparations are limited by rectal discomfort, diarrhoea, local pathology, and patient acceptance.

Parenteral Administration

In palliative care the subcutaneous route is a more acceptable form of parenteral administration than intravenous or intramuscular routes.

- Intravenous administration carries a higher risk of infection and phlebitis
- Intramuscular administration is painful and absorption is erratic

Subcutaneous administration produces a rapid response with 100% bioavailability.

Use small injection volumes to minimise pain.

Topical Preparations

Compounding a topical preparation or diluting an existing preparation may be acceptable where there is no commercial preparation available. Adequate facilities (e.g., scales) and trained staff are required. Potential risks include:

- Many formulations and expiry dates have not been scientifically established.
- Reliable stability information may be lacking.

And, if diluting commercial preparations (e.g., steroids), the following may be issues:

- Possible unpredictable chemical and/or physical interactions
- Decreased stability of active ingredient(s)
- Risk of biological spoilage during dilution, especially by *Pseudomonas aeruginosa*
- Dilution of the preservative system
- Dilution does not always have the corresponding effect on its potency (e.g., dilution of fluocinolone acetonide up to 1 in 10 produced no significant reduction in potency of vasoconstrictor effect).

Give extemporaneously prepared products the shortest practicable expiry and be vigilant for problems.

Pharmacology of Antiretroviral Drugs

Why Understanding ART Pharmacology is Important

As the rollout of antiretroviral therapy (ART) to those infected with HIV in developing countries begins, we are seeing a large number of people with late-stage HIV disease, some of whom may be considered terminally ill, being started on ART with the hope of recovering their health. According to local and international data up to 10% of people commencing ART in such previously untreated cohorts in the developing world will die within the first year of treatment (Sterne, 2005). This is due to the severe immune system damage of late stage HIV disease combined with high prevalence of OIs and underlying malnutrition (see Chapter 12: Integration of Palliative Care with ART).

These patients are usually already taking other medications, including prophylaxis or treatment of OIs and treatment of HIV-related symptoms such as peripheral neuropathy. Because drug interactions and adverse effects are common, treatment schedules need to be carefully selected and monitored to minimise problems. Some knowledge of the pharmacology of ARVs assists in the complex management of patients with late-stage HIV disease.

Brief Life Cycle of the HIV

After free HIV particles in the plasma fuse to a CD4 cell, viral RNA and key enzymes of viral replication are injected into the cell. Reverse transcriptase (RT) is a viral enzyme crucial to the process of HIV infecting a CD4 cell. The enzyme allows production of DNA from the single stranded viral RNA injected into the CD4 cell after fusion of the HIV with the cell membrane. The RT matches one of the 4 intracellular nucleotides, adenine (A), cytidine (C), thymidine (T), or guanine (G), to the nucleotides in the viral RNA chain and a complementary chain is created. The two chains spiral together to form DNA, which is inserted into the nucleus of the infected CD4 cell.

The protease enzyme is a second viral enzyme carried within the HIV particle and injected into the CD4 cell on fusion. This enzyme is involved in the cleaving of the regulatory proteins from immature viral protein precursors prior to the packing of viral particles to create a new virion. The completed viral particles bud off the CD4 cell and develop into their mature form in the plasma.

Brief Description of ART

Chapter 12: *Integration of Palliative Care into ART* provides a description of the core competencies and critical components to have in place in order to treat and monitor patients on ART. Readers are referred to their own national ART guidelines for their country-specific combinations of ARVs to use in ART. Use of standardised regimens is an essential component of the WHO recommendations for national ART programmes. The standardised regimen should include a first and a limited number of second line regimens, recognizing that individuals who cannot tolerate or fail the first and second line regimens would be referred for individualised care by specialist physicians. Table 11.1 and Figure 11.1 provide guidance from WHO for selection of drugs.

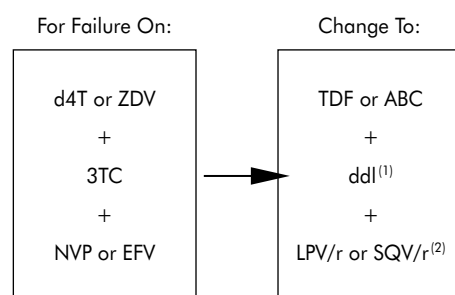
Table 11.1: First-Line ARV Regimens in Adults and Adolescents and Characteristics Which Can Influence Choice

ARV Regimen	Major Potential Toxicities	Usage in Women (In Childbearing Age or Who Are Pregnant)	Usage in TB Coinfection	Availability as Three Drug Fixed Dose Combination	Laboratory Monitoring Requirements
d4T/3TC/NVP	d4T-related neuropathy, pancreatitis, and lipodystrophy; NVP-related hepatotoxicity and severe rash.	Yes	Yes in rifampicin-free continuation phase of TB treatment. Use with caution in rifampicin-based regimens.	Yes	No
ZDV/3TC/NVP	ZDV-related GI intolerance, anemia, and neutropenia; NVP related hepatotoxicity and severe rash.	Yes	Yes in rifampicin-free continuation phase of TB treatment. Use with caution in rifampicin-based regimens.	Yes *	Yes
d4T/3TC/EFV	d4T-related neuropathy, pancreatitis, and lipodystrophy; EFV-related CNS toxicity and potential for teratogenicity.	No	Yes, but EFV should not be given to pregnant women or women of childbearing potential, unless effective contraception can be assured.	No. EFV not available as part of FDC. However partial FDC available for d4T/3TC *	No
ZDV/3TC/EFV	ZDV-related GI intolerance, anemia, and neutropenia; EFV-related CNS toxicity and potential for teratogenicity.	No	Yes, but EFV should not be given to pregnant women or women of childbearing potential, unless effective contraception can be assured.	No. EFV not available as part of FDC. However partial FDC available for ZDV/3TC.	Yes

Note: See footnotes in Appendix 2 for drug abbreviations.

* These combinations have been not pre-qualified by WHO, but could be used if assured quality formulations of proven bioequivalence are available.

Source: WHO, 2003.

Figure 11.1: Recommended Second-Line Regimens in Adults and Adolescents for Treatment Failure on First-Line ARV Regimens

⁽¹⁾ Dose of ddI should be reduced from 400 mg to 250 mg when co-administered with TDF.

⁽²⁾ LPV/r and SQV/r require secure cold chain. NVP can be considered as an alternative in resource-limited settings without cold chain.

Source: WHO, 2003.

Case Example: South African ART Roll-out Programme

ARVs used in the South African ART roll-out programme are used to illustrate the key factors in assembling a highly active antiretroviral therapy regimen and to explain clinically important pharmacological factors. South Africa has adopted a scheduled approach to ART in the public sector which minimises the number of drugs in use (see Box 11.3). The roll-out programme uses a non-nucleoside reverse transcriptase inhibitor (NNRTI)-based first line regimen; followed by a protease inhibitor (PI)-based regimen. (National Department of Health, South Africa, 2004) Only seven ARVs are used in the total management of adult patients, and a few more for paediatric patients.

Classes of Antiretrovirals (ARVs)

Three classes of ARVs are registered in South Africa to date:

- Nucleoside reverse transcriptase inhibitors
- Non-nucleoside reverse transcriptase inhibitors
- Protease inhibitors

Nucleoside Reverse Transcriptase Inhibitors (NRTIs)

This class consists of stavudine (d4T), lamivudine (3TC), zidovudine (AZT), didanosine (ddI), zalcitabine (ddC), and abacavir (ABC). Only stavudine, lamivudine, zidovudine, and didanosine are used in the expanded access programme in South Africa.

Mechanism of action: These drugs inhibit the reverse transcriptase enzyme. Each drug mimics one of the four cellular nucleotides. They are taken as DNA nucleoside analogues, which are then phosphorylated within the CD4 cell to become nucleotide analogues. Should an NRTI be selected by the reverse transcriptase in the process of producing viral DNA instead of a natural nucleotide, the DNA chain is terminated. NRTIs are usually given in pairs, as the backbone of a triple therapy regimen.

Giving two different NRTIs doubles the chance of the RT being inhibited. Giving two similar analogues confers no advantage (e.g., d4T and AZT), as they use the same thymidine kinase enzyme for phosphorylation (the rate-limiting step). Table 11.2 lists the nucleotide mimicked by each NRTI.

Table 11.2: Nucleotide Mimicked by NRTIs

NRTI	Nucleotide Mimicked	Use in SA ART Rollout (adult)
Stavudine (d4T)	Thymidine (T)	Regimen 1
Lamivudine (3TC)	Cytidine (C)	Regimen 1
Didanosine (ddI)	Adenine (A)	Regimen 2
Zidovudine (AZT)	Thymidine (T)	Regimen 2
Abacavir (ABC)	Guanine (G)	-
Zalcitabine (ddC)	Cytidine (C)	-

Table 11.3 lists the dosing, key side effects, and key drug interactions for each of the NRTIs. Giving NRTIs with similar adverse effect profiles should be avoided (e.g., peripheral neuropathy), particularly if the patient already experiences this problem. The major adverse effect of this class of drug is lactic acidosis.

Non Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)

There are two NNRTIs registered in South Africa, efavirenz (EFV) and nevirapine (NVP), both used in the first-line ART rollout regimen. They are used as part of a triple therapy regimen, usually with 2 NRTIs. NNRTIs have no additional benefits when given together, though increased toxicity is noted. (van Leth, 2004)

Mechanism of action: NNRTIs also inhibit reverse transcriptase. These drugs are structurally diverse, but both directly inhibit the catalytic site of the RT, again preventing the production of viral DNA.

Table 11.4 lists the dosing, key side effects, and key drug interactions for each of the NNRTIs.

Protease Inhibitors (PIs)

There are many protease inhibitors registered in South Africa, including lopinavir/ritonavir, ritonavir, nelfinavir, indinavir, and saquinavir. Lopinavir/ritonavir is the PI used in the second-line regimen of the South African ART roll out. PIs are usually used with 2 NRTIs to create a triple regimen.

Mechanism of action: PIs are potent inhibitors of viral replication. Inhibition of the protease enzyme prevents the development of mature viral proteins, and consequently complete, able virions cannot be formed.

Table 11.5 lists the dosing, key side effects, and key drug interactions for each of the PIs.

Table 11.3: NRTI Dosing, Side Effects, and Key Drug Interactions

NRTI	Dosing	Key Side Effects	Important Interactions
Stavudine	40 mg 12 hourly (30 mg if <60 kg)	Peripheral neuropathy, hepatic steatosis (monitor ALT), lactic acidosis	No added benefit when given with AZT
Lamivudine	150 mg 12 hourly	Diarrhoea, pancreatitis	No added benefit when given with ddC
Didanosine	400 mg once a day on waking — taken on a completely empty stomach, 45 mins to 1 hour before eating. (250 mg if <60 kg)	Pancreatitis, peripheral neuropathy, GIT effects (bloating, flatulence, nausea, diarrhoea), lactic acidosis	Soluble form contains antacid — do not give with drugs needing acid for absorption (e.g., ketoconazole)
Zidovudine	300 mg 12 hourly	Bone marrow suppression (anaemia, neutropaenia — monitor FBC), GIT symptoms, myopathy, lactic acidosis	No added benefit when given with d4T
Abacavir	300 mg 12 hourly	Hypersensitivity reaction in first 6 weeks in 3% (fever, rash, fatigue, GIT/respiratory symptoms. Can be fatal. Do not rechallenge). AVOID during PREGNANCY	
Zalcitabine	0.75 mg 8 hourly	Peripheral neuropathy (10%), stomatitis	No added benefit when given with 3TC

Table 11.4: NNRTI Dosing, Side Effects, and Key Drug Interactions

NNRTI	Dosing	Key Side Effects	Important interactions
Efavirenz	600 mg daily (usually given at night)	CNS disturbances in 1 st few weeks (dysphoria, distractedness, dizziness), GIT symptoms. AVOID in PREGNANCY (may cause neural tube defects)	Both induces and inhibits cytochrome p450 enzymes — avoid drugs using this system ^a . Possibly safe with rifampicin.
Nevirapine	200 mg daily for the first 2 weeks (induction dose), then 200 mg 12 hourly	Skin rash (16%), nausea, vomiting, hepatitis (8% risk if NVP started with CD4 >250; can be fatal)	Induces cytochrome p450 enzymes — avoid drugs using this pathway ^a .

a. Levels of drugs in this list may alter when given with any other in the list, resulting in either sub-therapeutic or toxic levels. Use together with care. Key cytochrome p450 inducers — rifampicin, phenytoin, carbamazepine; key inhibitors — fluconazole, ritonavir, erythromycin; key drugs which use the system — benzodiazepines, warfarin, oral contraceptives, statins.

Table 11.5: PI Dosing, Side Effects, and Key Drug Interactions

PI	Dosing	Key Side Effects	Important Interactions
Lopinavir/ritonavir	400/100 mg 12 hourly	GIT symptoms, lipid abnormalities, lipodystrophic changes ^b	Inhibits cytochrome p450 — avoid drugs using this system ^a .
Ritonavir	600 mg 12 hourly at full antiviral dose; 100 mg 12 hourly to boost another PI.	Bad taste, GIT symptoms, raised liver enzymes, lipodystrophic changes ^b	Potent inhibitor of cytochrome p450 — avoid drugs using this system ^a . Increases metabolism of oestrogen-containing contraceptives (use condoms!)
Nelfinavir	1250 mg 12 hourly	GIT symptoms, ongoing diarrhoea, lipodystrophic changes ^b	Inhibits cytochrome p450 — avoid drugs using this system ^a . Increases metabolism of oestrogen-containing contraceptives (use condoms!)
Saquinavir	Soft gel Hard gel	GIT symptoms, headache, raised liver enzymes, lipodystrophic changes ^b	Inhibits cytochrome p450 — avoid drugs using this system ^a .
Indinavir	800 mg 8 hourly when given alone. 800 mg 12 hourly with 100 mg ritonavir per dose.	GIT symptoms, renal stones (drink 2 L water daily), rash, lipodystrophic changes ^b	Inhibits cytochrome p450 — avoid drugs using this system ^a .

a. Levels of drugs in this list may alter when given with any other in the list, resulting in either sub-therapeutic or toxic levels. Use together with care. Key cytochrome p450 inducers — rifampicin, phenytoin, carbamazepine; key inhibitors — fluconazole, ritonavir, erythromycin; key drugs which use the system — benzodiazepines, warfarin, oral contraceptives, statins.

b. Lipodystrophy describes a group of metabolic changes resulting from long term use of the protease inhibitors and perhaps the NRTIs. Changes include: increased cholesterol and triglyceride levels, a shifting of body fat distribution (central obesity due to excess visceral fat, peripheral and facial wasting) and osteopaenia. There may be some reversal on stopping therapy.

Antiretroviral Therapy (ART)

No antiretroviral agent has shown sustained benefit when given alone. See Box 11.3 for the recommended South African combination of ARVs for effective ART. See Box 11.4 for other ART guidelines. The only drug used for monotherapy is AZT in short courses, of no more than 6 months (e.g., for prevention of mother-to-child transmission or post-exposure prophylaxis). A 6 – 12 month reduction in viral load (0.6 – 0.8 log) may be expected with monotherapy, but after this time the virus develops resistance to the drug and will grow through the therapy.

Dual therapy provides a longer benefit (perhaps 12 to 18 months with a 1.2 – 1.8 log drop in viral load), but again the virus eventually develops resistance to the agent used, with possible cross resistance to other agents in the same class.

Triple therapy, usually 2 NRTIs with either a non-nucleoside reverse transcriptase inhibitor or a protease inhibitor, is now standard of care and has been used since 1996. A 3 log drop in viral load can be maintained for 3 to 5 years or more. All patients commencing ART should be offered triple therapy for best outcome.

Box 11.3:**South African ARV Recommendations*****The South African National ART Rollout Recommends the Following:*****Schedule 1 – NNRTI based**

stavudine 40 mg 12 hourly
(30 mg if <60 kg)

lamivudine 150 mg 12 hourly

efavirenz 600 mg daily (for men or women on hormonal contraception)

OR nevirapine (for women of child-bearing potential)

Treatment should be commenced only in a person with WHO stage 4 HIV disease or a CD4 count of <200 cells/mL, who are socially and behaviorally ready for treatment.

Schedule 2 – PI based

zidovudine 300 mg 12 hourly

didanosine 400 mg daily
(250 mg daily if <60kg)

lopinavir/ritonavir 400/100 mg
12 hourly

Schedule 2 is used for patients who have failed a regimen 1 (i.e., patients with previously undetectable viral load who are noted to have 2 consecutive viral loads of >5000 copies/mL 3–6 months apart despite intensive adherence counselling).

Box 11.4:**HIV/AIDS Antiretroviral Treatment Guidelines**

An array of HIV/AIDS antiretroviral treatment guidelines have been developed—internationally and in-country. There are differences across them—due to when they were developed and updated as well as variations in treatment philosophy. Please check back on Web sites periodically to ensure you have the latest version as guidelines change frequently in response to new understanding about HIV/AIDS treatment and as new antiretroviral medications are introduced. See also section on ART treatment guidelines in Appendix 1.

Internationally Developed

World Health Organisation. WHO has developed various guidelines, including ART Guidelines in Resource Limited Settings. The 2006 version (a revision of the 2004 edition) covers ART in adults and adolescents, children, and prevention of mother-to-child transmission. See <http://www.who.int/hiv/en/> or contact vitoriam@who.int, Dr. Marco Vitoria, HIV/AIDS Department, WHO.

Country Specific

Listing of Various HIV/AIDS Treatment Guidelines. This site lists international and country-specific guidelines. The site is maintained by the University of California-San Francisco's HIVInsite. When reviewing guidelines listed here, make sure to check original source Web site to ensure that the version presented on HIVInsite is the latest version. See <http://hivinsite.ucsf.edu>

Following is a sampling of guidelines presented on this Web page.

- U.S. HIV/AIDS Care Guidelines. Developed under the auspices of the U.S. Department of Health and Human Services (DHHS), guidelines cover antiretroviral therapy (adults/adolescents, paediatrics, prevention of mother-to-child transmission) as well as prevention and treatment of opportunistic infections and other topics. See <http://aidsinfo.nih.gov/>; telephone: 1-800-448-0440; Fax: 1-301-519-6616; outside US: 1-301-519-0459. Live help line at http://aidsinfo.nih.gov/live_help/ or email at ContactUs@aidsinfo.nih.gov
- British HIV Association HIV Treatment Guidelines, 2005. See <http://www.bhiva.org/index.html> or eileen.witney@chelwest.nhs.uk
- National Antiretroviral Treatment Guidelines – 2004, South Africa Department of Health. See <http://www.doh.gov.za/docs/>

Other HIV/AIDS Antiretroviral and Care Resources

The following is a select list of resources and guides that cover HIV/AIDS antiretroviral treatment (e.g., aspects such as drug interactions or summaries of recommendations) as well as other HIV/AIDS care topics such as managing opportunistic infections.

- HIV Drug Interactions. This Web site reviews drug interactions such as antiretroviral-to-antiretroviral and interactions with anti-malarial drugs. Interactions are presented in chart formats. See <http://www.hiv-druginteractions.org>
- Handbook on Pædiatric AIDS in Africa (2004) was developed by the African Network for the Care of Children Affected by AIDS (ANECCA). Antiretroviral treatment is but one of multiple HIV care chapters presented. Download from <http://www.fhi.org/en/HIVAIDS/pub/guide/mans1.htm> (whole document or section by section) or www.rcqhc.org (entire document download only). For a hard copy, contact: Dr Denis Tindyebwa, Chairperson ANECCA, P O Box 29140, Kampala, Uganda, Phone 256-41-530888, Fax 256-41-530876, Email dtindyebwa@rcqhc.org or anecca@rcqhc.org
- Handbook of HIV Medicine (2002). Wilson, D et al. This document covers various HIV/AIDS care topics, including antiretroviral therapy. Available from Oxford University Press at +27 (0)21 596 2300 or through various book sellers.

Adherence

The success of triple therapy depends on the proportion of doses taken. From as early as 1998, clinical evidence showed an increased likelihood of viral suppression with improved adherence (Paterson, 2000). Missing as few as 3 doses a month (5%) can result in subtherapeutic levels of the ARV that may allow the eventual development of viral resistance.

Maintaining a 95% adherence to a 12-hourly regimen for many years is difficult. A patient must be motivated from the outset. Pre-treatment education and on-treatment support is crucial. Patients should be encouraged to join a support group and to take full responsibility for their therapy. A number of pre-treatment readiness education and counselling sessions should be offered prior to commencing a patient on ART.

Clinically Relevant Drug-specific Pharmacology

Absorption and Bioavailability

ddI is an acid-labile drug that is buffered with an antacid. It must be taken on a completely empty stomach three hours after eating and an hour before eating. Any acid from digestion can result in the drug not being absorbed.

Nelfinavir, saquinavir, and lopinavir are better absorbed if taken with a high-fat meal.

Ketoconazole requires acid for absorption. Late-stage HIV patients are often achlorhydric and may not absorb adequate drug.

Protease inhibitors: The cytochrome p450 enzyme system on the GIT wall is induced or inhibited as is the hepatic enzyme system. Other enzyme inducers may reduce the active drug available.

Metabolism

Dosing times: ARVs need to be dosed regularly, as prescribed, in order to maintain therapeutic drug levels. See Figures 11.2a and 11.2b.

Protease inhibitor boosting: Ritonavir is often used in low doses (100 mg) with other PIs. As it is a powerful inhibitor of both the GIT and hepatic cytochrome p450 system, ritonavir increases absorption and delays metabolism of the second drug. For example, 8 hourly 800 mg indinavir dosing may be reduced to 12 hourly 800/100 mg indinavir/ritonavir dosing. Lopinavir is the first PI to be combined with ritonavir in a fixed dose tablet (133 mg lopinavir/33 mg ritonavir). Ritonavir is not acting as an ARV at these doses.

Hepatic cytochrome p450 system: As mentioned in Box 11.1, drugs that inhibit, induce, or use the hepatic cytochrome p450 system should be used together with caution. Expert advice should be sought if use of two or more such drugs is unavoidable.

Figure 11.2a: Drug Levels With Eccentric Dosing

Eccentric dosing may result in times when drug levels are subtherapeutic.

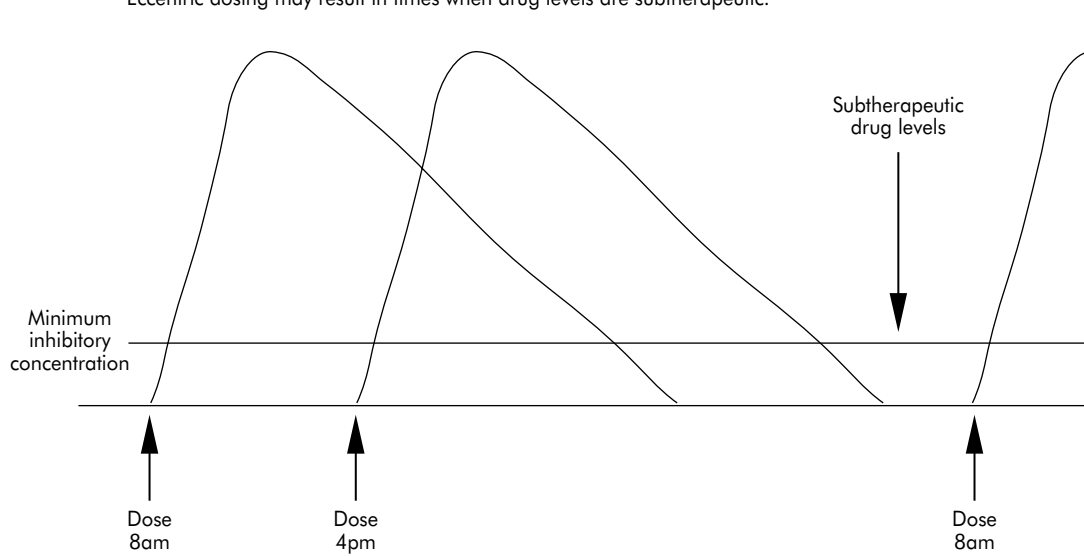
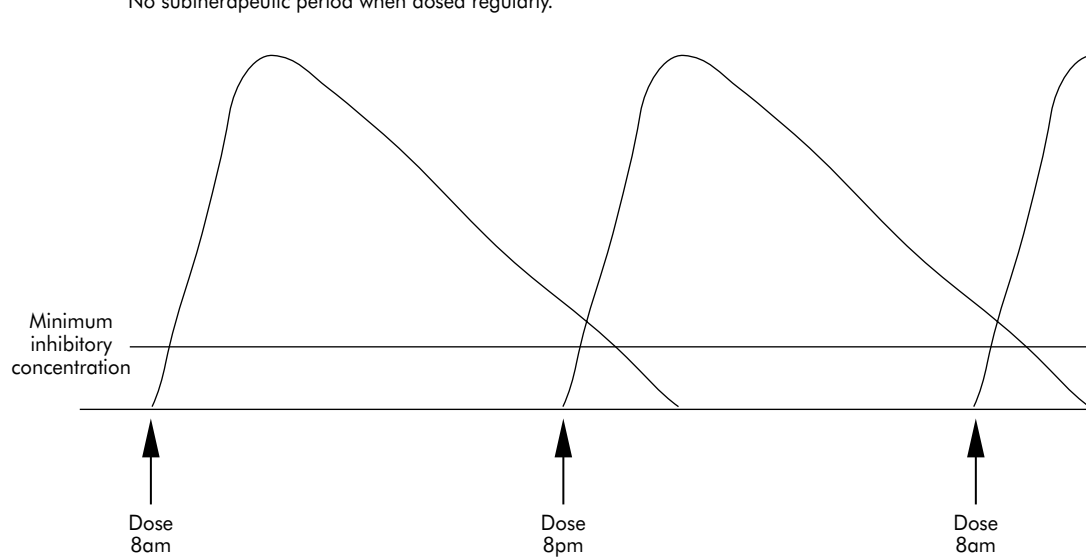


Figure 11.2b: Drug Levels With Regular Dosing

No subtherapeutic period when dosed regularly.



Drug Combinations

Practise caution when combining drugs:

- With a similar toxicity profile, as this may result in added toxicity (e.g., ddI and d4T [peripheral neuropathy]; AZT, aciclovir, and cotrimoxazole [bone marrow suppression], rifampicin and nevirapine [hepatitis])
- With similar or competing mechanisms of action (e.g., AZT and d4T, efavirenz and nevirapine)
- With a known harmful metabolic interaction (e.g., fluconazole and nevirapine [inhibition of p450 results in increased and potentially toxic nevirapine levels])

Conversely, drug interactions can be used to the benefit of the patients:

- With synergy (e.g., two different NRTIs like d4T and 3TC)
- With a known beneficial drug interaction (e.g., ritonavir and indinavir or lopinavir)

See Appendix 3 for drug interactions. Specifically, the following drugs for palliative care are a few of the ones that must be used with caution in patients on ART: phenytoin, carbamazepine, cimetidine, and phenobarbitone.

Interactions Between ART and Tuberculosis Treatment

Tuberculosis coinfection is common in HIV patients, and co-treatment with ART and TB treatment occurs frequently. Clinically significant drug interactions as well as additive side effects and drug toxicities exist between standard TB treatment and ART.

Rifampicin is a potent inducer of the cytochrome P450 enzyme system (particularly isoenzyme 3A4) increasing metabolism and reducing plasma levels of many hepatically metabolised drugs, including non-nucleoside reverse transcriptase inhibitors and PIs. This may result in treatment failure.

Rifampicin is a critical component of tuberculosis treatment. Rifabutin, an alternative to rifampicin, is extremely expensive, and is therefore not a practical option for TB therapy in resource-limited settings. It is therefore recommended that the ARV regimen be modified to make it compatible with standard, rifampicin-based TB treatment wherever possible. ART consisting of three nucleoside reverse transcriptase inhibitors is not recommended. Unlike rifabutin, rifampicin doses do not need to be adjusted when combined with ART.

Ritonavir, which is included in all PI options for coadministration of ART with rifampicin, causes gastrointestinal intolerance in many patients. Gradual dose escalation of the ritonavir dose over a period of one week may help improve tolerability in patients who experience nausea.

Table 11.6 gives NNRTI and PI options for use with rifampicin and suggests possible regimen modifications to make ART compatible with rifampicin.

TB treatment has specific risks in patients with HIV infection. Pyridoxine must be given to all HIV-infected patients taking TB treatment to reduce the risk of isoniazid-induced peripheral neuropathy. Patients who drink alcohol excessively are at increased risk of hepatotoxicity and peripheral neuropathy and should be counselled to decrease their alcohol intake. There is an additive risk of side effects and drug toxicity when ARVs and drugs used for treatment of TB are administered together. Shared side effects and toxicities are summarised in Table 11.7.

Table 11.6: Recommendations for Co-administering PIs and NNRTIs with Rifampicin

Single Protease Inhibitors		
	Recommended Dose When Combined with Rifampicin	Comments and Alternative Regimens
Ritonavir	600 mg 12 hourly	Ritonavir is poorly tolerated in adults because of GIT side effects, and is therefore not commonly used as a single PI
Amprenavir	Rifampicin should not be used together with these single PIs	Change the regimen to make it compatible with rifampicin, taking the patient's previous antiretroviral regimen into account (do not use a drug that the patient has previously failed). Options include substituting these drugs with efavirenz 600 mg or 800 mg daily, or lopinavir/ritonavir 400/400 mg 12 hourly, or saquinavir/ritonavir 400/400 mg 12 hourly.
Indinavir		
Nelfinavir		
Saquinavir		
Boosted PI Combinations		
	Recommended Dose When Combined with Rifampicin	Comments
Saquinavir / ritonavir	Saquinavir 400 mg + ritonavir 400 mg 12 hourly	Limited clinical experience
Lopinavir / ritonavir	Lopinavir 400 mg + ritonavir 400 mg 12 hourly	Additional ritonavir must be added to the lopinavir/ritonavir fixed dose combination in order to achieve these doses. Limited clinical experience. Monitor closely for hepatotoxicity.
Non-nucleoside Reverse Transcriptase Inhibitors		
	Recommended Dose When Combined with Rifampicin	Comments
Efavirenz	Either 600 mg or 800 mg/day	Increased central nervous system side effects may occur with the 800 mg dose.
Nevirapine	200 mg twice daily	There may be an increased risk of hepatotoxicity when nevirapine is administered together with TB treatment, particularly during the first 3 months of nevirapine-containing ART.

Source: Cohen, 2004. Reprinted with permission. Based on CDC updated guidelines, 2004

Table 11.7: Shared Side Effects of TB and ART Drugs

Side effect	Antiretroviral	Treatment for TB
Nausea	didanosine, zidovudine, ritonavir	pyrazinamide
Hepatitis	nevirapine, efavirenz	rifampicin, isoniazid, pyrazinamide
Peripheral neuropathy	stavudine, didanosine	isoniazid
Rash	nevirapine, efavirenz	rifampicin, isoniazid, pyrazinamide

Source: Cohen, 2004. Reprinted with permission.

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