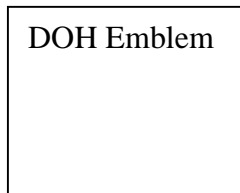


# Anti-Retroviral Therapy in South Africa

A pocket guide on the prevention and management of Side  
Effects and Drug Interactions



FIRST EDITION

# Anti-Retroviral Therapy in South Africa

## A pocket guide on the prevention and management of Side Effects and Drug Interactions

DOH Emblem



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This pocket guide serves as a quick reference source for clinicians, in the management of patients on antiretroviral drugs to complement treatment guidelines as outlined in the Comprehensive Plan for HIV and AIDS Care, Management and Treatment. This booklet is a companion to other detailed guidelines already available and it is to be used as a quick reference by trained healthcare workers. Information in the pocket guide will be revised as necessary to reflect the dynamic nature of HIV and AIDS treatment.

**Disclaimer:** The Department of Health or the authors accept no responsibility for errors or omissions. This pocket guide must be used in conjunction with the National Antiretroviral Treatment Guidelines and other references.

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## PREFACE

The first edition of “A pocket guide of the prevention and management of Side Effects and Drug Interactions” in South Africa provides an easy and quick reference to assist the prescribers and those responsible for clinical management of HIV and AIDS on the effective management of side effects and drug interactions that are most common.

This is an evolving area, and as new information becomes available about drug interactions between different medicines and antiretroviral drugs, as well as safety information from the pharmacovigilance programme, further updates on a regular basis will be published. The Pharmacovigilance programme is aimed specifically at collecting data from local settings where antiretroviral therapy will be used.

This text gives an outline of side effects, dosage regimen, and treatment for adverse drug reactions in algorithms that are easy to follow. This reference must be read taking cognizance of the published “National Antiretroviral Treatment Guidelines”.

Therapeutic regimens that have been selected for triple combination antiretroviral are limited to the public sector comprehensive plan for the treatment, care and support of HIV and AIDS. Although not exhaustive, more such publications will be available to support antiretroviral therapy and the safety management of these therapeutic agents in the private sector.

The safety monitoring tools provided will serve as a sound basis to provide good safety standards. It is envisaged that active reporting will be encouraged and a new culture created of reporting and sharing experiences for better patient care and management.

Ms. M. P. Matsoso  
Registrar of Medicines  
Medicines Control Council (MCC)

## **ACKNOWLEDGEMENTS**

The treatment of HIV, AIDS and opportunistic infections involves the use of several drugs. In South Africa, a significant number of people use also alternative, complementary and traditional medicines. The use of such a myriad of drugs calls for some guidance on rational drug use, as well as on preventing and managing adverse effects, drug interactions and medications errors.

It is with pleasure that the National Department of Health wishes to acknowledge and thank all the members of the writing team and contributors for developing such a much needed handbook.

**Dr. R. Mulumba**

Acting Chief Director and Cluster Manager: HIV, AIDS, and TB

## ACRONYMS AND ABBREVIATIONS

3TC	Lamivudine
AIDS	Acquired Immune Deficiency Syndrome
ANC	Antenatal care
ART	Antiretroviral treatment
ARV	Antiretroviral
AZT	Zidovudine
D4T	Stavudine
ddl	Didanosine
EDL	Essential drugs list
EFV	Efavirenz
HAART	Highly active antiretroviral therapy
HBC	Home Based care
HIV	Human Immunodeficiency Virus
INH	Isoniazid
LPV	Lopinavir
M&E	Monitoring and evaluation
MCH	Maternal and child health
MTCT	Mother-to-child transmission
NNRTI	Non-nucleoside reverse transcriptase inhibitor
NRTI	Nucleoside reverse transcriptase inhibitor
NVP	Nevirapine
PEP	Post-exposure prophylaxis
PI	Protease inhibitors
PMTCT	Prevention of mother-to-child transmission
RTV	Ritonavir
TLC	Total lymphocyte count
VCT	Voluntary counselling and testing



## Section 1: ARVs regimens for drugs on the National Formulary

### 1.1. Adult Regimens

Table 1: Adult regimens

Regimen	Drugs
1a	Lamivudine (3TC) + Stavudine (d4T) + Efavirenz
1b	Lamivudine (3TC) + Stavudine (d4T) + Nevirapine
2 (second Line)	Didanosine (ddl) + Zidovudine (ZDV) + Lopinavir/Ritonavir

*For full dosing, consult the "National Antiretroviral Treatment Guidelines"*

#### A. Antiretroviral naïve adult patients

Unless contraindicated, all patients will commence therapy on:

1. Stavudine (d4T) 40 mg every 12 hours (or 30 mg every 12 hours if < 60 kg), with
2. Lamivudine (3TC) 150 mg every 12 hours, and
3. Efavirenz (EFV) 600 mg at night (or 400 mg if < 40 kg) OR Nevirapine (NVP) 200 mg daily for the first 2 weeks increasing to 200 mg every 12 hours after this.

Note:

Ensure reliable contraception in women of childbearing age (preferably injectable contraceptive and use of barrier method). If unable to guarantee reliable contraception, Nevirapine will be substituted for Efavirenz. Extra safety bloods will need to be taken as per Table 2.

#### B. Antiretroviral non-naïve patients

Patients who have been previously exposed to antiretroviral therapy are to be discussed with a clinical expert before a treatment regimen is commenced.

- Those patients controlled on their antiretroviral medication should continue on their treatment or swap to the appropriate treatment protocol
- Those who stopped treatment for any reason but who were controlled, it is important to establish the reasons for interruption, provide adherence counselling, and resume therapy under close monitoring
- Those who have failed a previous regimen should be started on drugs they have not been exposed to before and to which there is little likelihood of cross resistance as judged by a clinical expert.
- Women and children who are eligible for antiretroviral therapy and whose only exposure to antiretroviral drugs, previously was nevirapine used prevention of maternal to child transmission (PMTCT) may have developed resistance to both nevirapine and efavirenz. For these women, there is also a need to seek clinical guidance.

- In general, clinical guidance could be obtained by contacting the HIV/AIDS Clinicians Helpline: 0800 122 322

Figure 1:

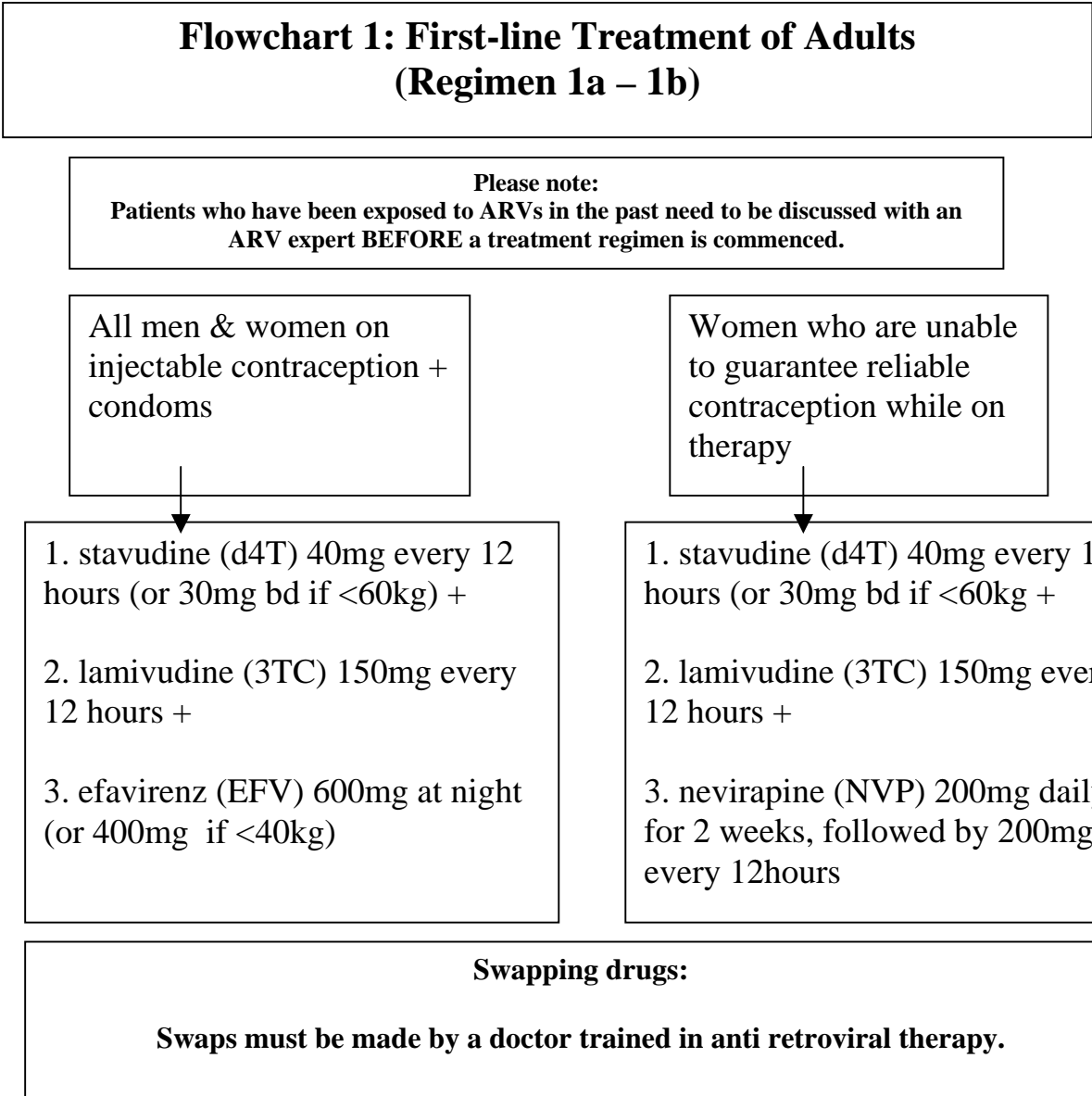
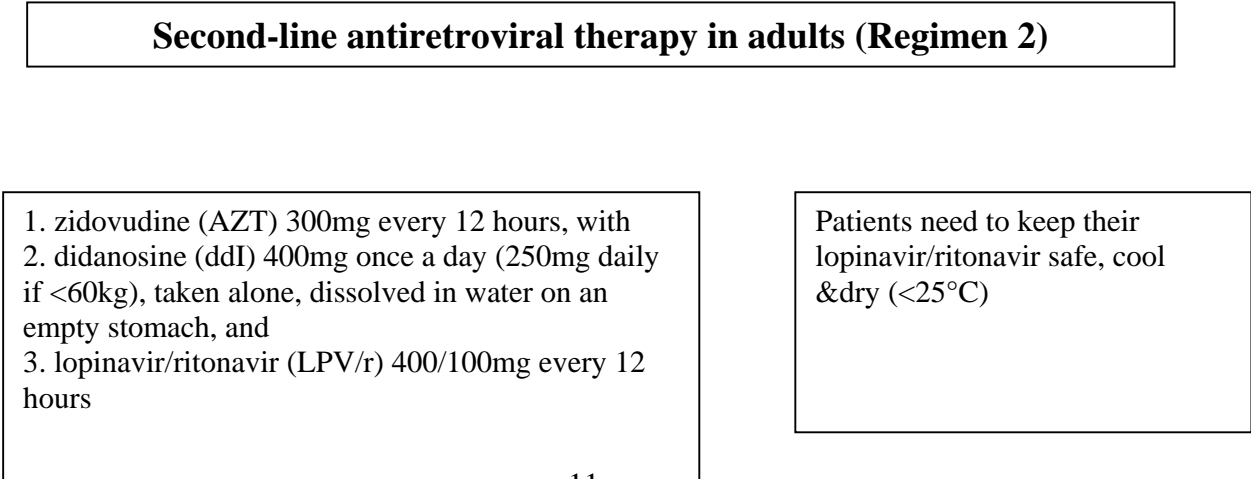


Figure 2:



## 1.2. Pediatric Regimens

Table 2: Pediatric regimens

<i>First line</i>	
6months-3yrs old	Lamivudine (3TC) + Stavudine (d4T) + Lopinavir/Ritonavir
>3yrs old and > 10kg	Lamivudine (3TC) + Stavudine (d4T) + Efavirenz
<i>Second Line</i>	
6months-3yrs old	Didanosine (ddl) + Zidovudine (ZDV) + Nevirapine
>3yrs old and > 10kg	Didanosine (ddl) + Zidovudine (ZDV)+ Lopinavir/Ritonavir

For full dosing, consult the "National Antiretroviral Treatment Guidelines".

- All infants under 6 months of age who require treatment with antiretroviral therapy should be started on treatment under specialist supervision
- Stavudine solution requires refrigeration. If no fridge available, stavudine capsules may be opened and dissolved, and the required amount administered to the child. The rest can be discarded
- Kaletra is recommended for children under 3 years because it is assumed that most children in this age group would have received nevirapine for PMTCT. Resistance mutations have been shown to occur in a significant number of children exposed to nevirapine in this fashion. Most resistance mutations have been shown to fade within the first year. It is still unknown whether children with resistance mutation will have archived resistance and therefore inadequate response to therapy with a regimen including an NNRTI. Kaletra (Lopinavir/ritonavir) needs to be kept cool (< 25° C)
- Didanosine must be taken alone, on an empty stomach, at least an hour before (or 2 hours after) a meal. Tablets should be dissolved in at least 30 ml of water. It is important to use 2 tablets of didanosine e.g if child needs 100mg prescribe 2x50mg tablets.
- Drugs not listed in the 1<sup>st</sup> and 2<sup>nd</sup> line regimens such as ritonavir, nelfinavir, saquinavir, abacavir, nevirapine may be available at tertiary care centres.

Table 3: Paediatric dosages per body surface area

Body surface (m <sup>2</sup> )	Volume (ml) of each dose MORNING / 12hrs later	Volume (ml) of each dose MORNING / 12hrs later	Amount per dose MORNING / 12hrs later
	ZIDOVUDINE 10 mg/ml syrup	RITONAVIR 80 mg / ml syrup	DIDANOSINE 25, 50, 100 mg tablets
0.30	5.5 ml	1.5 ml	25 mg
0.35	6.0 ml	1.75 ml	25 mg
0.40	7.0 ml	2.0 ml	25 mg
0.45	8.0 ml	2.25 ml	25 mg
0.50	9.0 ml	2.5 ml	50 mg
0.55	10.0 ml	2.75 ml	50 mg
0.60	11.0 ml	3.0 ml	50 mg
0.65	12.0 ml	3.25 ml	50 mg
0.70	13.0 ml	3.5 ml	50 mg
0.75	13.5 ml	3.75 ml	75 mg
0.80	14.5 ml	4.0 ml	75 mg
0.85	15.0 ml	4.25 ml	75 mg
0.90	16.0 ml	4.5 ml	75 mg
0.95	17.0 ml	4.75 ml	75 mg
1.00	18.0 ml	5.0 ml	75 mg
1.05	19.0 ml	5.25 ml	100 mg
1.10	20.0 ml	5.5 ml	100 mg
Up to 1.4 BSA			CONTINUE 100 mg EVERY 12 HRS UP TO 1.4 BSA

Table 4: Paediatric dosages per body weight

Weight (kg)	Volume (ml) of EACH dose MORNING / 12 HRS LATER	Volume (ml) of EACH dose MORNING / 12 HRS LATER	Volume (ml) of EACH dose MORNING / 12 HRS LATER		Volume (ml) of EACH dose MORNING / 12 HRS LATER	Amount (mg) of ONE DOSE ONLY (bedtime)
	STAVUDINE (d4T) 1 mg / ml syrup	LAMIVUDINE (3TC) 10 mg / ml syrup	NEVIRAPINE 10 mg / ml		ABACAVIR 20 mg / ml	EFAVIRENZ 50 and 200 mg caps
	TWICE	TWICE	1-14 DAYS ONCE	AFTER 14 DAYS TWICE	TWICE	ONCE
4	4 ml	1.5 ml	1.5 ml	3.0 ml	1.6 ml	
5	5 ml	2.0 ml	2.0 ml	3.5 ml	2 ml	
6	6 ml	2.5 ml	2.5 ml	4.0 ml	2.4 ml	
7	7 ml	3.0 ml	3.0 ml	5.0 ml	2.8 ml	
8	8 ml	3.0 ml	3.0 ml	5.5 ml	3.2 ml	
9	9 ml	3.5 ml	3.5 ml	6.0 ml	3.6 ml	
10	10 ml	4.0 ml	4.0 ml	7.0 ml	4 ml	200 mg
11	11 ml	4.5 ml	4.5 ml	8.0 ml	4.4 ml	200 mg
12	12 ml	5.0 ml	5.0 ml	8.5 ml	4.8 ml	200 mg
13	13 ml	5.0 ml	5.0 ml	9.0 ml	5.2 ml	200 mg
14	14 ml	5.5 ml	5.5 ml	10.0 ml	5.6 ml	200 mg
15	15 ml	6.0 ml	6.0 ml	10.5 ml	6 ml	250 mg
16	16 ml	6.5 ml	6.5 ml	11.0 ml	6.4 ml	250 mg
17	17 ml	7.0 ml	7.0 ml	12.0 ml	6.8 ml	250 mg
18	18 ml	7.0 ml	7.0 ml	12.5 ml	7.2 ml	250 mg
19	19 ml	7.5 ml	7.5 ml	13.5 ml	7.6 ml	250 mg
20	20 ml	8.0 ml	8.0 ml	14.0 ml	8 ml	300 mg
21	21 ml	8.5 ml	8.5 ml	15.0 ml	8.4 ml	300 mg
22	22 ml	9.0 ml	9.0 ml	15.5 ml	8.8 ml	300 mg
23	23 ml	9.0 ml	9.0 ml	16.0 ml	9.2 ml	300 mg
24	24 ml	9.5 ml	9.5 ml	17.0 ml	9.6 ml	300 mg
25	25 ml	10.0 ml	10.0 ml	17.5 ml	10 ml	350 mg
26	26 ml	10.5 ml		18.0 ml	10.4 ml	350 mg
27	27 ml	11.0 ml		19.0 ml	10.8 ml	350 mg
28	28 ml	11.0 ml		19.5 ml	11.2 ml	350 mg
29	29 ml	11.5 ml		20.0 ml	11.6 ml	350 mg
30	30 ml	12.0 ml		20.0 ml	12 ml	350 mg
31	30 ml	12.0 ml		20.0ml	12.4 ml	350 mg
32	30 ml	13.0 ml		20.0ml	12.8 ml	350 mg
33	30 ml	13.5 ml		20.0ml	13.2 ml	400 mg
34	30 ml	13.5 ml		20.0ml	13.6 ml	400 mg
35	30 ml	14.0 ml		20.0ml	14 ml	400 mg
36	30 ml	14.5 ml		20.0ml	14.4 ml	400 mg
37	30 ml	15.0 ml		20.0ml	14.8 ml	400 mg

NB: Please note that Abacavir doses should be rounded to the equivalent doses of Lamivudine.

## Section 2: Side Effects of ARV Drugs

*Prevention and management of side effects from drugs used to manage HIV and AIDS remain a challenge to clinicians, patients, drug regulators, researchers, government, health care workers, family members and all those affected. Acute and long term side effects, mild to severe (sometimes fatal) reactions continue to affect patient decisions to start treatment, continue treatment, and adhere to prescribed regimens. The clinician is also faced with the task of, selecting the right regimen, educating or counseling the patient on possible side effects (prevention and management strategies) and monitoring to ensure that benefits always outweigh the risk. A brief description and algorithms for the management of common/severe adverse reactions with the regimens for the treatment of HIV on the national formulary have been outlined for quick reference.*

### **2.1. Efavirenz-Side Effects**

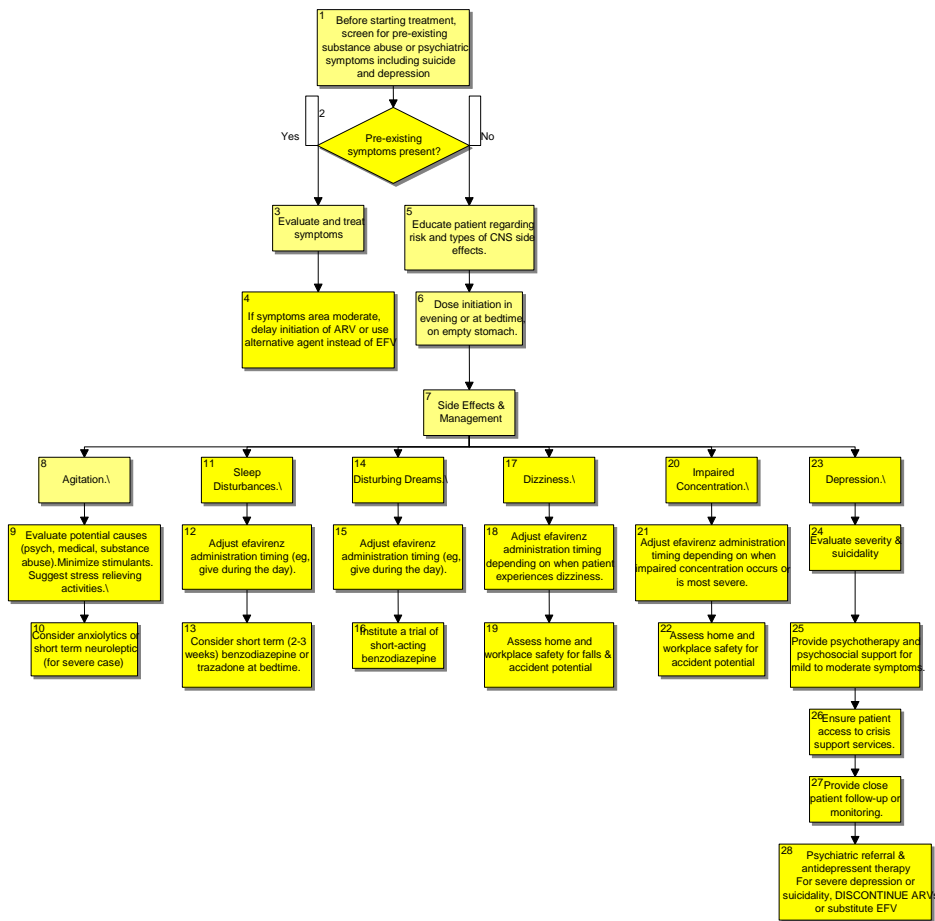
Efavirenz is a potent NNRTI that acts by noncompetitive inhibition of HIV-1. CNS side effects have been reported in more than 53% of people taking Efavirenz in some studies, with the most common ones being dizziness, insomnia, impaired concentration, somnolence, abnormal dreams and hallucinations. These side effects occur during the first 2 days of treatment and last for several hours after each dose. Efavirenz neurologic symptoms are self limiting and generally resolve without treatment by the 4<sup>th</sup> week, but can persist as mild symptoms for a longer time. These CNS effects can be aggravated by psychoactive drugs or alcohol. Also manic and paranoid reactions as well as severe depression. Skin rash has been reported up to 27% of patients but the most severe grade is limited to less than 5% which could be Steven-Johnson syndrome.

According to Barlett and Gallant (2004), when initiating treatment with Efavirenz:

- Prepare the patient: Screen and stabilize preexisting neuropsychiatric (NP) symptoms
- Educate the patient: Regarding most common NP side effects
- Reassure the patient: About Efavirenz' effectiveness and the severity of its side effects which are usually mild to moderate and of limited duration.
- Treat: Address new and persistent side effects since early and effective management of CNS side effects in the patient taking Efavirenz is imperative to improve patient outcomes.

**Reminder:** *Efavirenz is contraindicated in women who are pregnant or breast-feeding; patients on psycho-active drugs. Patients with history of psychiatric disturbances and seizures should be monitored closely.*

Management of Efavirenz-related CNS Side Effects  
(adapted from: Canadian J of Infect Dis: July/August 2001, Volume 12, Number C)

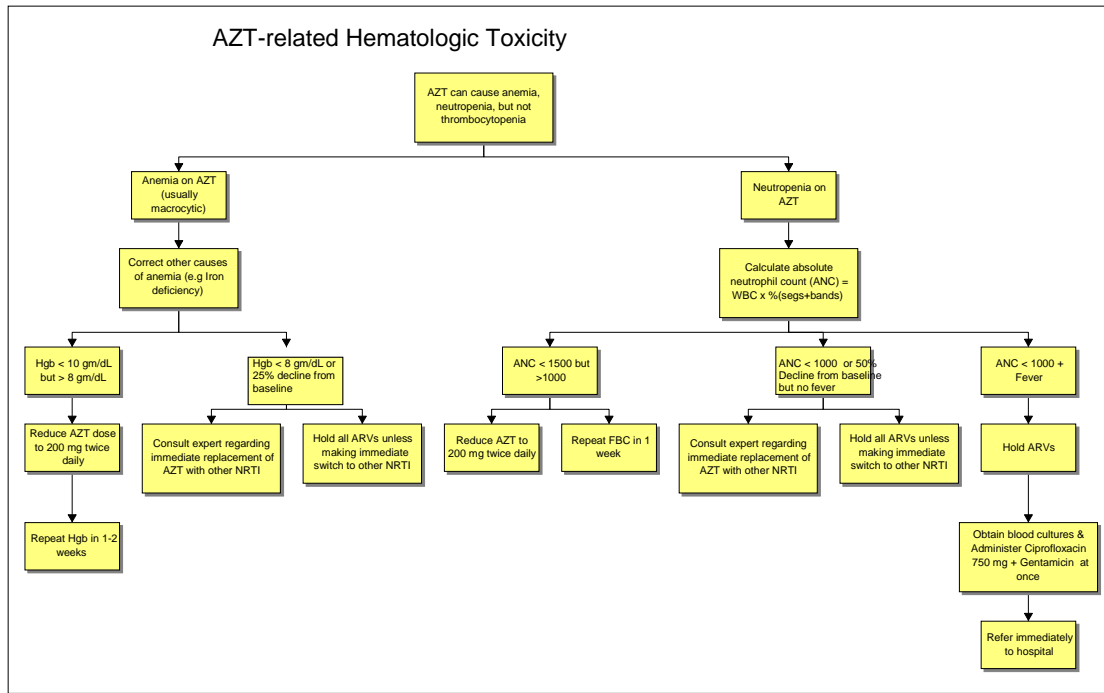


## 2.2. AZT-Induced haematological Side Effects

Zidovudine, a NRTI was the first antiretroviral to be approved for the treatment of patients with HIV. Common adverse reactions with AZT include, *headache, malaise, myalgia, anorexia, nausea, anemia and neutropenia*. 5-10% of people taking AZT develop Anemia according to some studies. Predisposing factors include, advanced stage of HIV infection, concurrent myelosuppressive agents or chemotherapy. Anemia can be seen as early as 4 to 6 weeks after initiation of AZT. Hemoglobin levels are usually used to evaluate the extent and progress of AZT-induced anemia.

Neutropenia occurs less frequently than anemia. Neutropenia usually occurs within 12 to 24 weeks of initiating AZT. Neutrophil count can be used as a marker to determine the extent of AZT-induced neutropenia. Predisposing factors also include, advanced stage of HIV infection and concomitant myelosuppressive drugs. Granulocytopenia (very rarely thrombocytopenia) has also been reported with AZT treatment.

## AZT-related Hematologic Toxicity



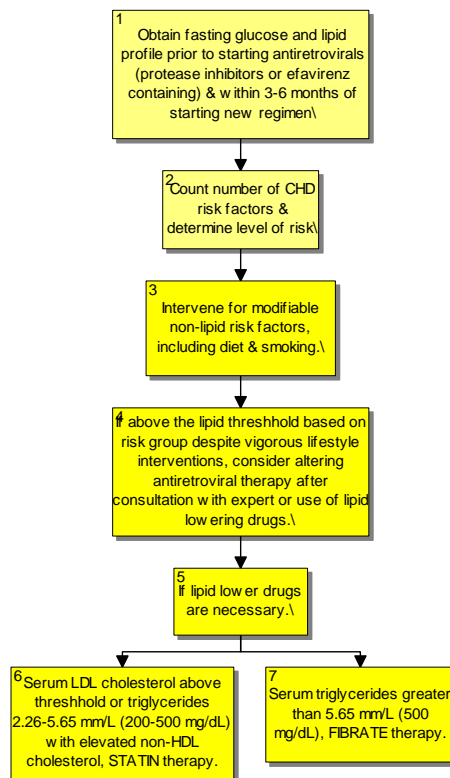


### 2.3. Dyslipidemia (Lipid Abnormalities)

This is primarily reported with the Protease Inhibitors but have also been reported with the NRTIs and NNRTIs. Increases in total cholesterol are usually due to PIs. NNRTIs are also known to increase total cholesterol but have also been reported to increase HDL particularly Efavirenz. It is prudent to obtain a fasting baseline serum lipid profile before initiating ART and take levels after 3 months. Other levels may then be requested as clinically indicated depending on previous levels, cardiovascular risk factors or symptoms. Life style modifications such as increased exercise, proper nutrition, weight loss, avoidance of illicit drugs and alcohol and smoking cessation are all important measures to take to prevent or decrease lipid abnormalities.

#### Dyslipidemia Management

(adapted from Dube et al. Clinical Infectious Diseases 2003; 37:613–27)



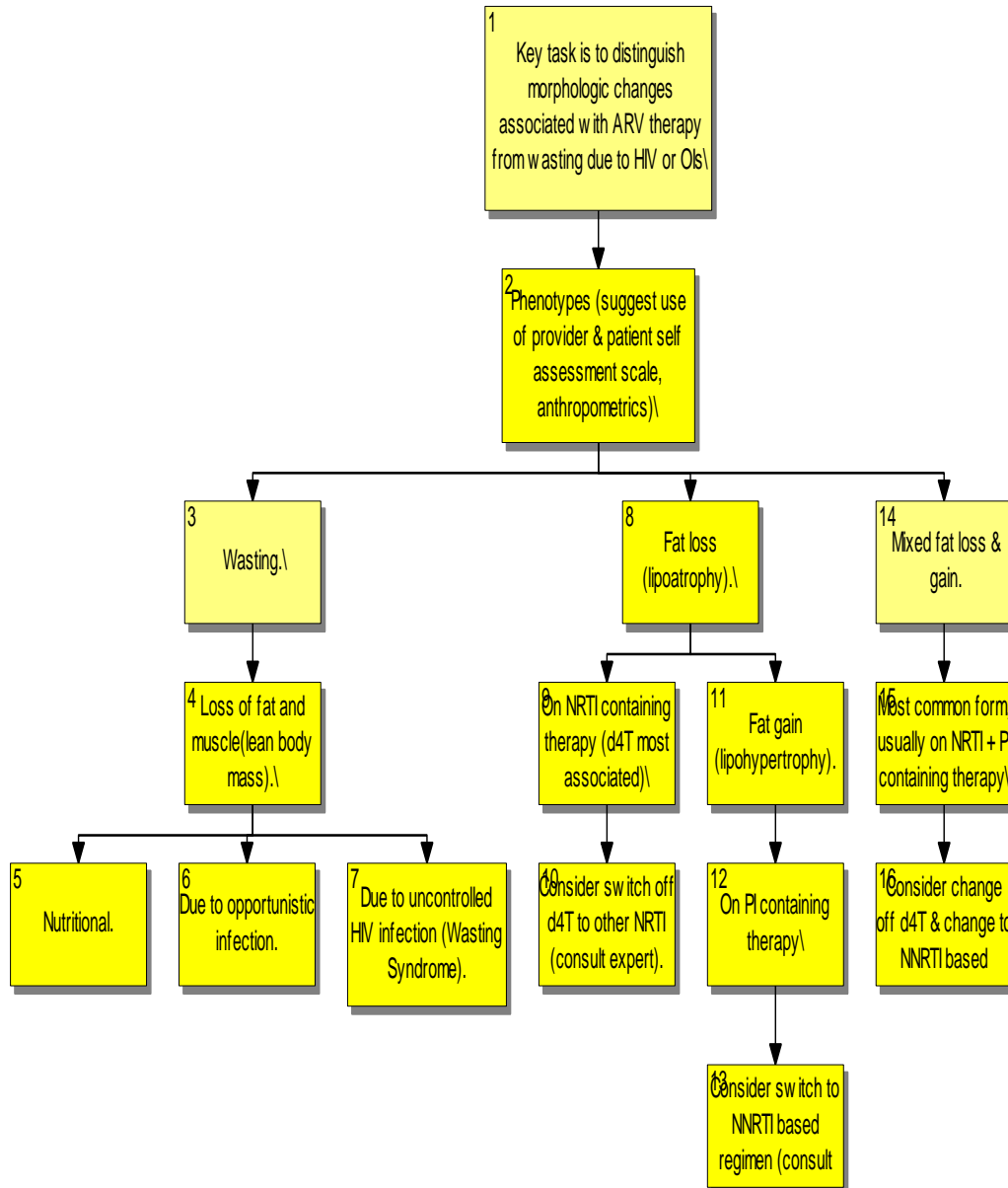


#### *2.4. Lipodystrophy*

Fat redistribution has been reported with ART and typically involves, accumulation of visceral fat in the abdomen (central obesity), dorsocervical area (buffalo hump) and breasts, loss of subcutaneous fat in the face, extremities and buttocks.

Patients with fat redistribution should be screened for glucose (diabetes mellitus and glucose intolerance) and lipid metabolism (high levels of triglycerides, total cholesterol, LDL cholesterol, low HDL cholesterol) disorders. It is important that clinicians should monitor and recommend regular exercise, proper nutrition and provide psychological support where necessary due to body habitus changes. Various treatment strategies should be applied depending on the underlying cause.

# Lipodystrophy Management



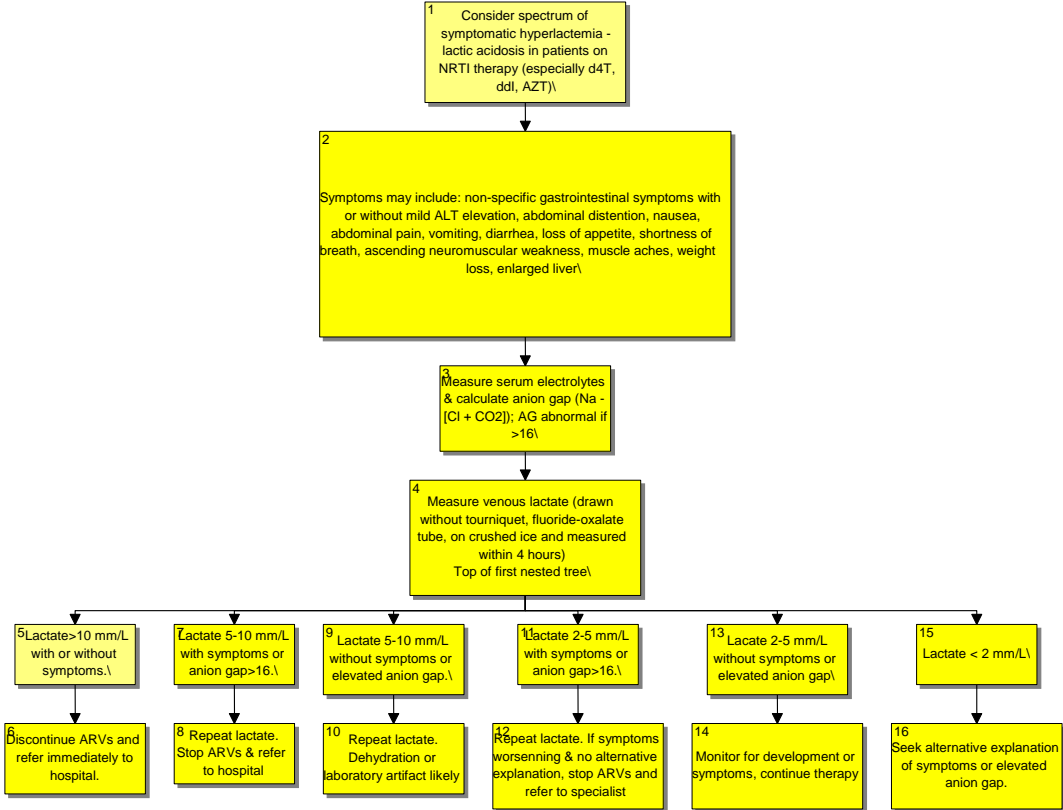
## 2.5. Lactic Acidosis

Lactic acidosis is a rare but life threatening condition and usually occurs in 1 to 20 months after start of NRTI therapy. Clinical symptoms are non-specific and include, fatigue, nausea, vomiting, abdominal pain, weight loss and dyspnea. These symptoms may occur acutely or gradually over time. A blood test usually will show elevated levels of lactate with or without metabolic acidosis. A complete evaluation should include an arterial blood gas, serum amylase and lipase levels and liver function tests. Asymptomatic hyperlactatemia occurs more frequently, in about 15% of patients on NRTIs based on some studies. Routine monitoring of serum lactate is not indicated nor recommended in patients with asymptomatic hyperlactatemia. Levels should however be taken immediately if patient is symptomatic

and complains of fatigue, has sudden weight loss, abdominal disturbances, nausea, vomiting and sudden dyspnea. Potential risk factors include female sex, obesity, prolonged exposure to NRTI (especially D4T, DDI, or DDC), acute infection and pregnancy. Due to the fatality that has been reported with lactic acidosis, such cases must be handled by or referred to experienced clinicians. The reason for high mortality relates to the fact that the diagnosis is usually made late as clinicians treat these patients for presumed P. pneumonia and think of lactic acidosis only when the patient fails to respond to treatment. Therefore patients suffering from lactic acidosis should be referred to Hospital for inpatient care since it persists for days even after the offending drugs have been discontinued.

### Management of Lactic Acidemia

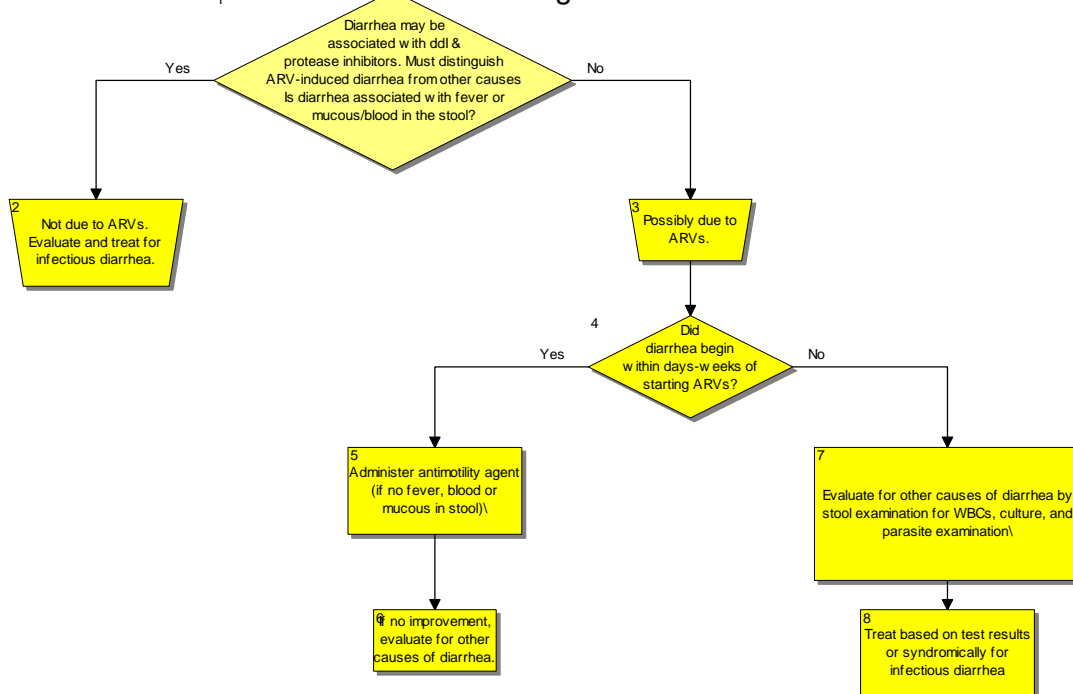
(Adapted from Carr, A., Clinical Infectious Diseases 2003; 36(Suppl 2):S96–100)



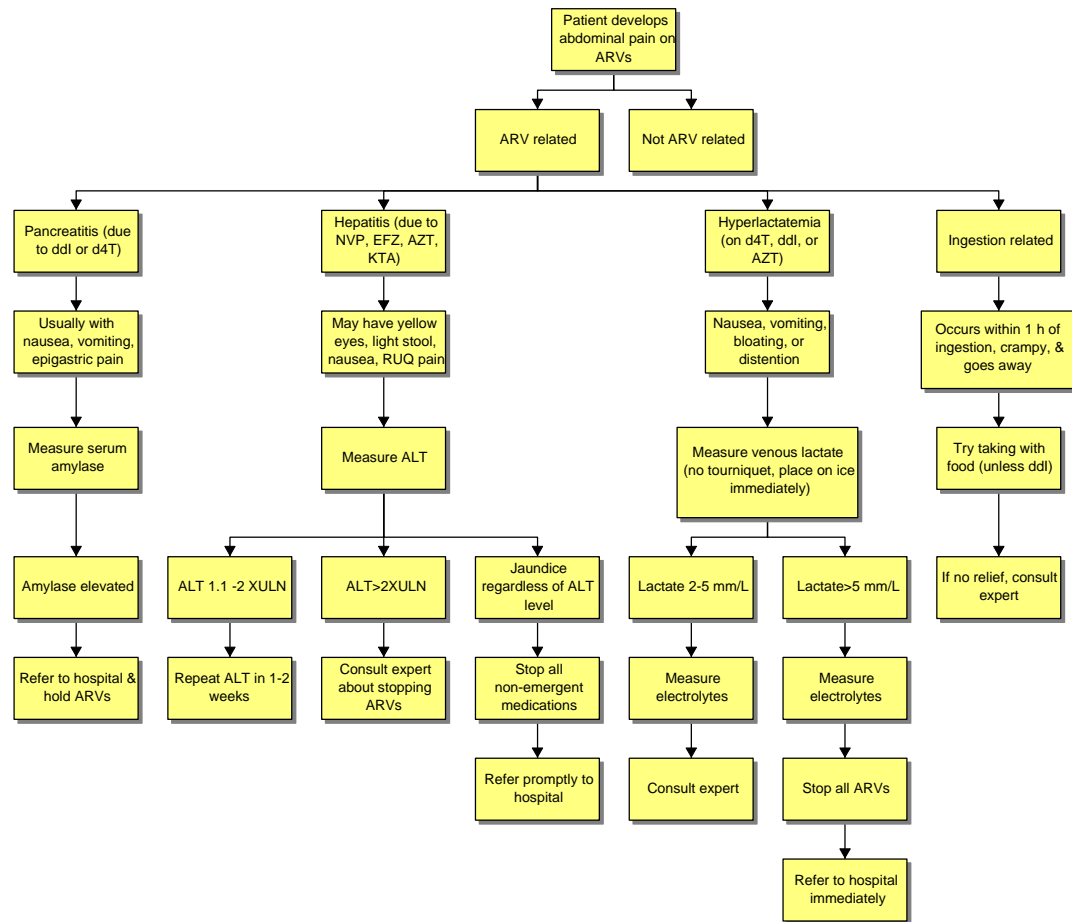
## 2.6. Gastrointestinal side effects

Abdominal discomforts are the most commonly reported side effects with ARVs and may occur earlier on in therapy. Common patient complains include, abdominal discomfort, nausea and vomiting, loss of appetite, diarrhea, abdominal pain, pancreatitis, constipation and heartburn. Patients should be informed that most gastrointestinal symptoms are self-limiting but some can linger for some time or reappear and could be a sign of a serious condition. GI side effects can be a nuisance and greatly impact drug therapy outcome and the patient's quality of life. GI side effects can cause dehydration, electrolyte imbalances, weight loss and malabsorption leading to low plasma drug levels. Coffee, smoking, spicy food, unknown herbal medicines and non-steroidal anti-inflammatory products should be avoided as much as possible. A workup should be done to diagnose the underlying cause or complication of GI problems in order to take proper corrective measures. If diarrhea occurs, make sure it is not of an infectious origin or lactose intolerance.

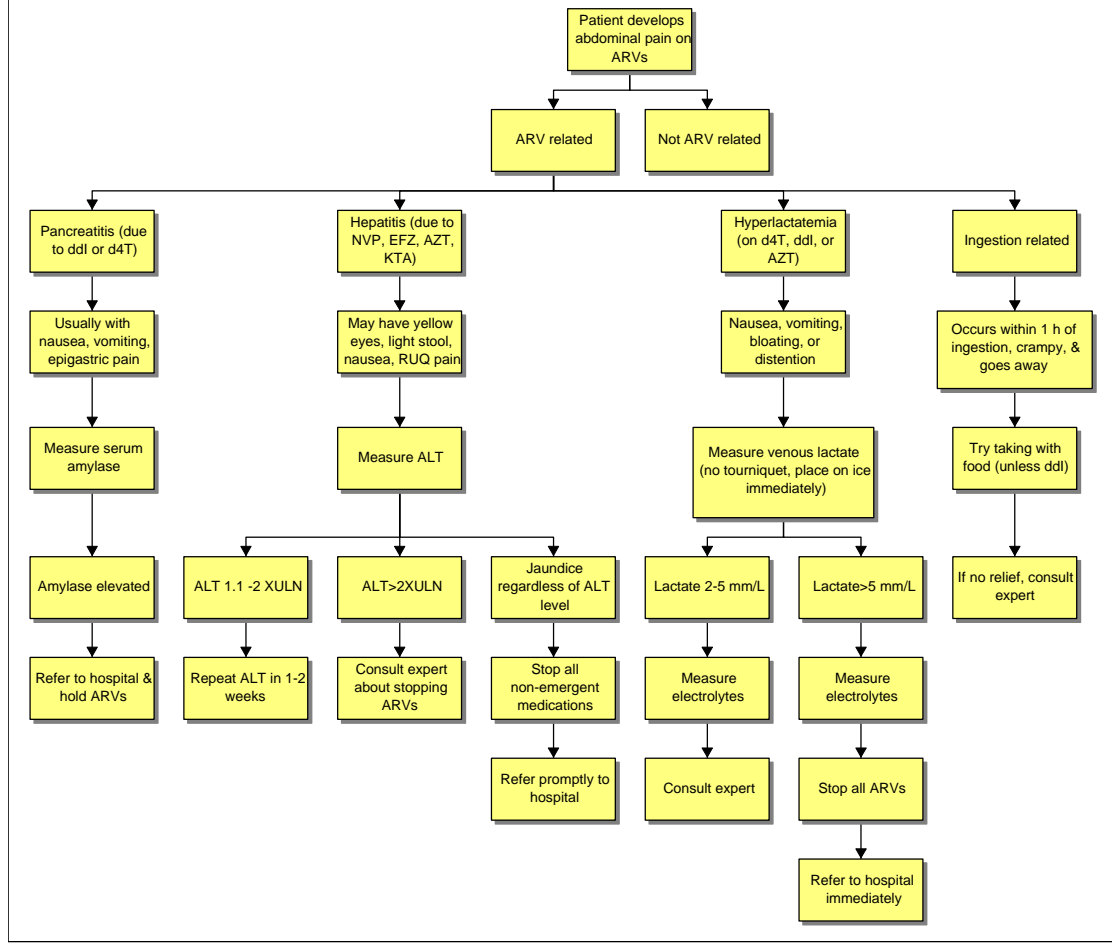
### ARV-associated Diarrhea Management



## ARV-related Abdominal Pain Management Flow Chart



## ARV-related Abdominal Pain Management Flow Chart

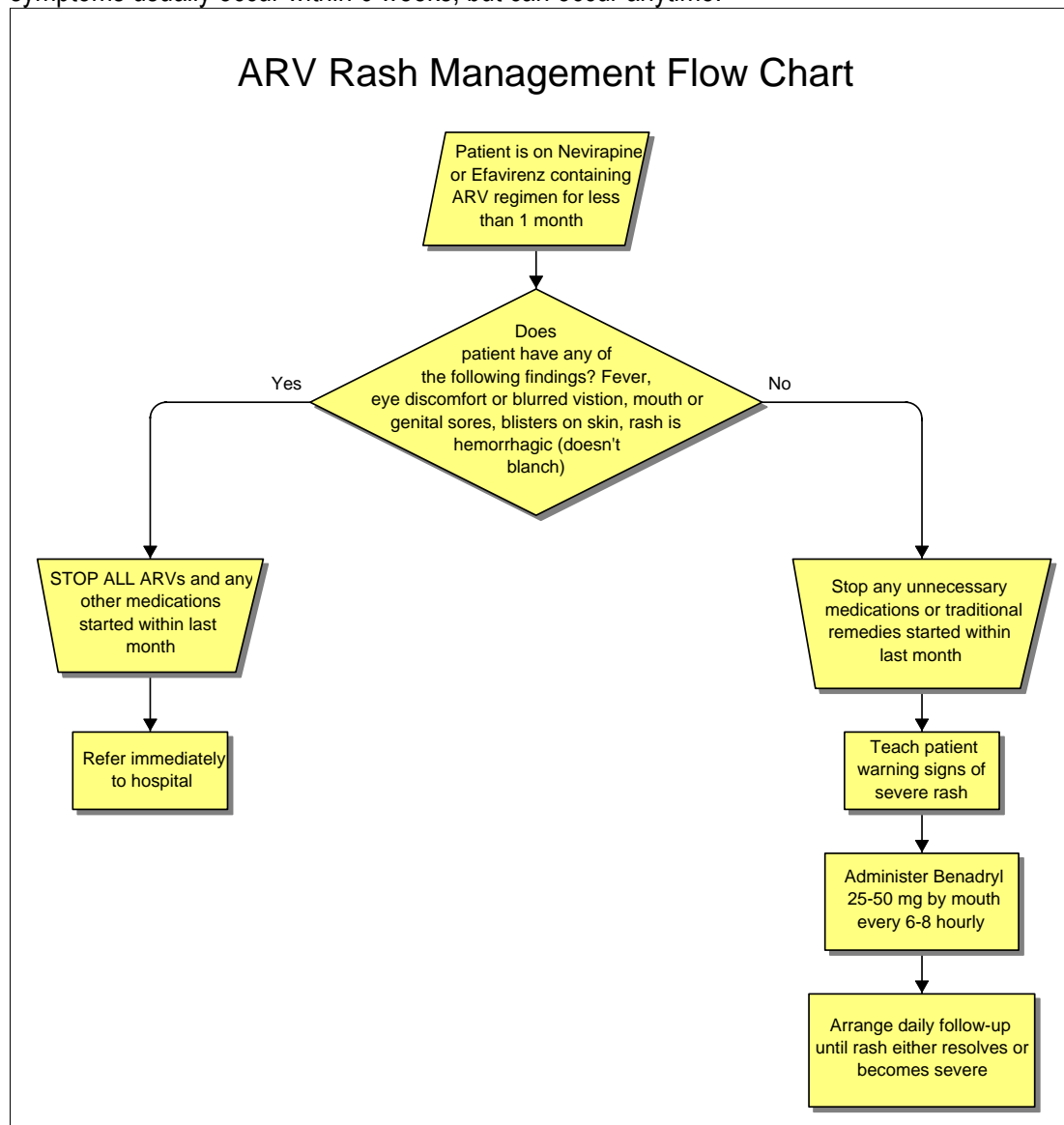




## 2.7. Allergies

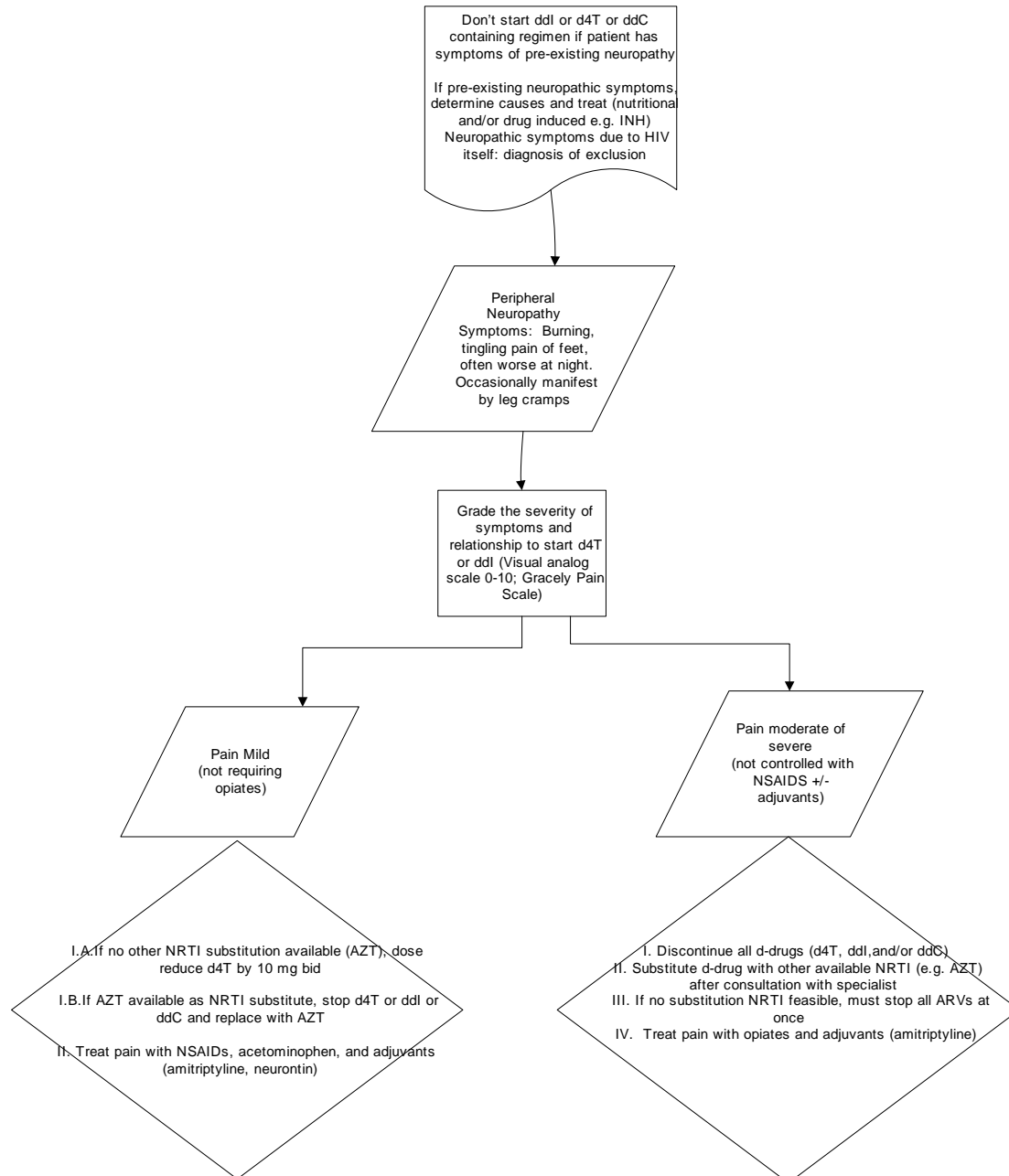
Allergies are a common occurrence with drug therapy. It however occurs more frequently in the HIV population than in the Non-HIV patients. Rashes can occur with all ARVs but more common with Nevirapine, Efavirenz and Abacavir. Allergy with Nevirapine and Efavirenz usually occurs within the second or third week of treatment. It is usually an erythematous, maculopapular, pruritic, and confluent rash distributed over the trunk and arm. Fever may precede the rash. Further symptoms include myalgia, fatigue and mucosal ulceration. Severe but rare reactions such as Steven Johnson syndrome, toxic epidermal necrolysis and hepatitis have been reported and will need prompt intervention by an expert if it occurs.

Abacavir causes a hypersensitivity reaction (HSR) in 5-10% of patients which can be fatal. HSR is not dose dependent and usually involves multiorgan systems. Abacavir HSR is characterized by fever and usually accompanied by general malaise, nausea, vomiting, diarrhea and abdominal. Rash may occur but is often mild. Abacavir must be discontinued and rechallenge is contraindicated. (Hoffman et al) symptoms usually occur within 6 weeks, but can occur anytime.



## 2.8. Distal Symmetric Polyneuropathy (DSP)

It usually presents with a distal symmetric distribution and sensorimotor paralysis. Numbness or burning dysesthesia of the distal extremities occurs at times with sharp shooting pains or continuous severe burning. Signs of DSP include depressed ankle reflexes, abnormal vibratory pinprick and cold sensations in the feet. Risk factors for DSP include, vitamin B12 deficiency, diabetes mellitus, history of alcohol abuse, and neurotoxic drugs such as isoniazid (INH), history of DSP and advanced HIV/AIDS. DSP is associated with several NRTIs with Zalcitabine > Didanosine > Stavudine > Zidovudine.





## Section 3: Drug Interactions

### 3.1. Drug-Drug Interactions

Drug interactions have become an increasingly complex challenge for clinicians treating HIV-infected patients.

Generally, drug interactions can be classified into two broad categories:

- interactions altering pharmacokinetics
- interactions affecting pharmacodynamics

Although both have the potential to be problematic in patients receiving HAART, pharmacokinetic interactions are more common and more difficult to predict due to the complex nature of drug metabolism. Most interactions are minor and may not be noticeable or of any clinical significance; however there are equally a significant number of interactions that can cause a decrease in patient or clinical outcomes, therapeutic failures, mild to moderate toxicity and severe to life threatening toxicities. Clinically significant drug interactions are generally those that produce at least a 30% change in pharmacokinetic parameters.

Drug interactions occur in almost all patients who are being treated for HIV/AIDS due to the average number of drugs (for HIV and opportunistic infections), food interactions, vitamins, complementary and herbal or traditional medicines that the patient may be taking.

#### A. Pharmacokinetic Interactions

Pharmacokinetic drug interactions can be classified according to whether they affect the absorption, distribution, metabolism, or elimination of other drugs. Most common drug interactions encountered in HIV infection involve those that affect metabolism or absorption.

##### *Metabolism*

Drug interactions involving metabolism are the most common and difficult to predict. Drugs used in HAART, especially NNRTIs and PIs, are metabolized via the cytochrome P450 enzyme system (CYP450). The CYP450 enzyme system is responsible for drug metabolism. The enzyme responsible for the majority of drug metabolism is CYP3A4, although 2C19 and 2D6 are also common and, to a lesser extent, CYP1A2. Drugs interact with CYP450 enzymes in one of three ways:

- through inhibition,
- through induction,
- by acting as a substrate

Some drugs may interact in more than one way and act as an inhibitor and inducer of different CYP450 enzymes. CYP450 enzymes are expressed both in the liver and in the enterocytes of the small intestine. They could produce inhibition or induction of drug metabolism within the gastrointestinal tract. A common example of this type of interaction is concurrent use of saquinavir and grapefruit juice. As a result of CYP450 inhibition in the GI tract, grapefruit juice significantly increases the bioavailability of saquinavir. Similarly, ritonavir may inhibit CYP3A4 in the intestine, which is one of the proposed mechanisms that contributes to this drug acting as a pharmacokinetic “boost.”

Drugs that inhibit CYP450 enzymes generally lead to decreased metabolism of other drugs metabolized by the same enzyme. The decreased metabolism can result in higher drug levels and increased potential for toxicity. Although inhibition is usually reversible, irreversible inhibition of CYP450 can occur, requiring new CYP450 enzyme to be synthesized to overcome the inhibition. Inhibition of drug metabolism tends to occur quickly (based on drug half-life), with maximal effect occurring when highest concentrations of the inhibitor are reached. Inhibition could be used therapeutically; for example ritonavir is a very potent inhibitor of CYP3A4, thus it is used in combination with Lopinavir (Kaletra) to increase Lopinavir blood levels. It is important to note that grapefruit juice contains various substances that inhibit CYP3A4-mediated metabolism in the gut wall.

Induction of the CYP450 system results in the increased clearance of concomitant medications metabolized by the same enzyme. When drugs that induce CYP450 enzymes are administered to a patient, the body responds by increasing the production of specific enzymes of the CYP450 system. The increased enzyme production could lead to increased metabolism and decreased concentrations of drugs metabolized via the same pathway. In general, the maximal effect of enzyme induction is apparent within 7 to 10 days, although with drugs with a relatively long half-life, such as methadone, the full effect of induction may take even longer. Drugs may also undergo a phenomenon termed “autoinduction”, whereby a drug has the capability of inducing its own metabolism. For example, nevirapine is such a drug that is why it is dosed 200 mg daily for the first 14 days of treatment, then 200 mg twice daily thereafter. A drug may act as a substrate by occupying the active site of a specific CYP450 enzyme. This drug’s metabolism is then affected by other medications that either induce or inhibit the CYP450 enzyme system.

**Absorption**

Drug interactions that affect absorption occur when one drug reduces the bioavailability of a second drug. Reduced absorption is caused by one of four mechanisms:

- alterations related to the presence or absence of food
- alterations in gastric pH caused by antacids, H2-blockers, or PPI
- chelation of drug caused by calcium, magnesium, or iron
- inhibition of the P-glycoprotein or other transport pump

**B. Pharmacodynamic Interactions**

Pharmacodynamic interactions occur when one drug causes an alteration in the pharmacological response (drug effect) of a second without a resultant change in drug concentrations or pharmacokinetic parameters. In this type of interaction, the pharmacological response from the drug can be antagonistic, additive, or synergistic.

- Antagonistic effects result in the drug’s pharmacological effect being reduced due to concurrent therapy, such as is seen when zidovudine and stavudine are co-administered.
- Additive effects occur when the use of two drugs leads to enhanced pharmacological activity
- Synergy occurs when the use of two or more drugs concurrently results in an effect that is greater than the addition of all of the drugs together (i.e., the effect is exponential, not additive)

Table 5: Enzyme induction or inhibition of some ARV Drugs			
<i>Drug</i>	<i>Enzyme Substrate</i>	<i>Will inhibit</i>	<i>Will induce</i>
Efavirenz	3A4, 2B6	3A4, 2C9/19	3A4
Nevirapine	3A4, 2B6		3A4, 2B6
Lopinavir	3A4	3A4, 2D6	
Ritonavir	3A, 2D6	3A, 2D6	1A2, 3A, 2C9

ARV Drug	Interacting drug	Effect of interaction	Clinical significance	Management
Abacavir	Alcohol	Decreased abacavir metabolism by alcohol dehydrogenase. Abacavir AUC: increased 41%; half-life: increased 26%	●NCS	No dose adjustment necessary
Abacavir	Zidovudine	Abacavir decreases the absorption of zidovudine. Reduced Cmax	●NCS	No dose adjustment necessary
Abacavir	Lamivudine	Abacavir decreases the absorption of lamivudine. Reduced Cmax	●NCS	No dose adjustment necessary
Didanosine (ddi)	Tetracyclines	Magnesium and calcium ions contained in the tablet's buffer chelate with the antibiotics	●PCS	Administer ddi at least two hours after or six hours before tetracycline
Didanosine (ddi)	Atazanavir	The buffer in didanosine neutralizes the acid environment needed for Atazanavir absorption	●PCS	Didanosine buffered tablets should be taken two hours after or one hour before taking Atazanavir to minimize the interaction or use enteric coated tablets
Didanosine (ddi)	Tenofovir	The ddi AUC increases by 60%	●PCS	Patients taking drugs concurrently require dosage reductions according to their weight: >60kg: 250mg; <60kg:200mg;if severely underweight give 125mg ddi once daily
Didanosine (ddi)	Allopurinol	Inhibition of presystemic metabolism by allopurinol. AUC of ddi increased between 113%-122%. Cmax increased 69-116%. Increased ddi effects (pancreatitis ,neuropathy)	●PCS	Monitor patient for ddi side effects
Didanosine (ddi)	Ciprofloxacin	Chelation and adsorption of ciprofloxacin by divalent and trivalent ions contained in the ddi buffer. AUC decreased 16% Cmax decreased 28%.	●PCS	Administer ciprofloxacin at least 2 hours after didanosine suspension
Didanosine (ddi)	Foods	Decreased didanosine effects due to a reduction in bioavailability by 20-25% when given with any food	●PCS	Administer ddi at least 2 hours apart with meals

Didanosine (ddi)	Itraconazole	Decreased itraconazole absorption due to decreased gastric acidity resulting from antacid buffer contained within didanosine tablets/suspension. Decreased itraconazole effects	●PCS	Administer itraconazole capsules at least 2 hours after didanosine tablets/suspension. Itraconazole solution as suggested alternative
Didanosine (ddi)	Ranitidine	Inhibition of gastric acid slightly enhancing didanosine bioavailability by reducing acid degradation. Ranitidine AUC: decreased 16%; Cmax: no significant change	●NCS	No dose adjustment necessary
Didanosine (ddi)	Metrocloramide	No significant change to didanosine levels	●NCS	No dose adjustment necessary
Didanosine (ddi)	Loperamide	Didanosine AUC: no significant change; Cmax: decreased 23%.	●NCS	No dose adjustment necessary
Didanosine (ddi)	Ketoconazole	Decreased ketoconazole absorption due to decreased gastric acidity resulting from antacid buffer contained within didanosine tablets/suspension. Possibly decreased didanosine effects.	●PCS	Administer didanosine tablets/suspension at least 2 hours apart
Didanosine (ddi)	Ganciclovir	Decreased oral ganciclovir absorption due to decreased gastric acidity resulting from antacid buffer contained within didanosine tablets/suspension. Didanosine AUC: increased 111%. Ganciclovir AUC: decreased 21%	●PCS	Administer didanosine tablets/suspension at least 2 hours apart of oral ganciclovir administration
Efavirenz	Midazolam and triazolam derivatives	In vitro studies suggest that efavirenz is a potent inhibitor of CYP3A4. There is a potential for increased drug concentrations of these medications and associated toxicity.	●PCS	Caution required; monitor patients for side effects of midazolam
Efavirenz	Clarithromycin	Concurrent use causes the clarithromycin AUC and Cmax to be decreased by 39% and 26% respectively	●CSI	Avoid concurrent use of the two drugs. Clinicians may consider using azithromycin instead, as CYP450 drug interactions are unlikely with this medication
Efavirenz	Methadone	Efavirenz is a CYP3A4 inducer therefore leading to reduced methadone levels as methadone is metabolized by the same isoenzyme. Effects are seen after about one to two weeks or longer.	●PCS	When using the two drugs concurrently monitor the patients for signs and symptoms of methadone withdrawal. Any change in antiretroviral therapy regimens should be reported to the providers

Efavirenz	Rifampicin	Concurrent use of efavirenz with rifampicin has been shown to reduce the AUC and Cmax of efavirenz by 26% and 20% respectively.	●PCS	Consult with experts before considering the options below. Increase efavirenz dosage to 800mg daily. Substitute rifampicin with rifabutin. Current guidelines suggest that rifabutin dose be increased to 450mg daily and the efavirenz should remain 600mg once daily.
Efavirenz	Phenytoin	Phenytoin induces the CYP450 system, blood drug levels of efavirenz maybe reduced.	●PCS	Concurrent use of the two drugs should be avoided if possible
Efavirenz	Phenobarbital	induces the CYP450 system .Reduced drug levels of efavirenz	●PCS	Concurrent use of the two drugs should be avoided if possible
Efavirenz	Indinavir	Both the indinavir and the efavirenz affect the CYP3A4 system, blood levels of indinavir maybe reduced	●PCS	Consult with experts before considering the options below. Increase indinavir dosage to 1000mg every eight hours
Efavirenz	Amprenavir	The amprenavir and the efavirenz have an antagonistic effect on the CYP3A4 system. Reduced doses of the amprenavir occur.	●PCS	Standard dose for efavirenz. Increase amprenavir dosage to 1,200mg three times daily
Efavirenz	lopinavir	The lopinavir and efavirenz have an antagonistic effect on the CYP3A4 system. The lopinavir levels may be reduced	●PCS	Consult experts before considering the options below: Standard dose for efavirenz; Increase lopinavir dose to 533mg/133mg (four capsules) twice daily.
Efavirenz	Ritonavir	The ritonavir and efavirenz have an antagonistic effect on the CYP3A4 system. The ritonavir levels may be reduced	●PCS	Consult experts before considering the options below: Standard dose for efavirenz. Increase ritonavir dose to 533mg/133mg (four capsules) twice daily
Efavirenz	Antacids	No significant effects	●NCS	No dosage adjustment is necessary
Efavirenz	Carbamazepine	Not studied. Induction of CYP450 and CYP3A4 by both drugs may lead to decreased efavirenz	●PCS	Avoid concurrent use. Consider alternative agents. Monitor carbamazepine levels and adjust dosage accordingly
Efavirenz	Ergotamine	Inhibition of CYP450 3A4 by efavirenz would result in increased ergotamine effects (e.g., ergotism).	●CSI	Do not co-administer

Efavirenz	Fluconazole	Inhibition of CYP450 3A4 by fluconazole. Efavirenz AUC: increased 16%; Cmax: no significant change	●NCS	No dose adjustment necessary
Efavirenz	Itraconazole	Induction of CYP450 3A4 by efavirenz results in decreased itraconazole effects	●CSI	Do not co-administer
Efavirenz	Lorazepam	Lorazepam AUC: no significant change; Cmax: increased 16%	●NCS	No dose adjustment necessary
Efavirenz	Phenobarbital	Induction of CYP450 3A4 by Phenobarbital results in decreased efavirenz effects	●PCS	Avoid combination if possible; consider alternative agents; monitor phenobarbital levels and adjust dosage accordingly. Suggested alternatives: Gabapentin, Lamotrigine; Topiramate
Efavirenz	St John's wort	Induction of CYP450 3A4 by St. John's wort results in decreased efavirenz effects	●CSI	Do not co-administer
Efavirenz	Warfarin	Possible inhibition or induction of CYP450 by efavirenz resulting in increased or decreased warfarin effects (altered INR, increased risk of bleeding or clotting)	●PCS	Monitor INR or PT and adjust warfarin's dosage accordingly
Efavirenz	Phenytoin	Induction of CYP450 3A4 by both drugs. Decreased efavirenz and phenytoin effects.	●CSI	Avoid combination if possible; consider alternative agents; monitor phenytoin levels and adjust as indicated. Suggested drug substitutes are: Gabapentin Lamotrigine, Topiramate
Efavirenz	Ketoconazole	Induction of CYP450 3A4 by efavirenz. Decreased ketoconazole effects	●CSI	Avoid concomitant administration
Efavirenz	Azithromycin	Azithromycin AUC: no significant change; Cmax: increased 22%.	●NCS	No dose adjustment necessary
Efavirenz	Clarithromycin	Inhibition of CYP450 3A4 by efavirenz. Clarithromycin AUC: decreased 39%; Cmax: decreased 26%; 14-hydroxy clarithromycin AUC: increased 34%; Cmax: increased 49%	●PCS	Dose adjustment not established
Efavirenz	Ethinyl Oestradiol	Ethinyl estradiol AUC: increased 37%; Cmax: no significant change.	●NCS	No dose adjustment necessary

Lamivudine	Cotrimoxazole	Lamivudine AUC: increased 44%. Increased lamivudine effects	●NCS	No dose adjustment necessary
Nevirapine (NVP)	Methadone	NVP is a CYP3A4 inducer therefore leading to reduced methadone levels as methadone is metabolized by the same isoenzyme. Effects are seen after about one to two weeks or longer.	●PCS	When using the two drugs concurrently monitor the patients for signs and symptoms of methadone withdrawal. An increase in methadone levels may be necessary after the addition of nevirapine
Nevirapine (NVP)	Oral contraceptives	Contraceptive failure may occur due to induction of CYP3A4 by NVP which increases metabolism of the oral contraceptive.	●PCS	Use an alternative birth control method
Nevirapine (NVP)	Rifampicin	Rifampicin and rifabutin are potent CYP3A4 inducers which reduce NVP trough levels by 37% and 16% respectively	●PCS	In patients taking anti-mycobacterial therapy substitute rifampicin with rifabutin to minimize reduction in nevirapine drug levels.
Nevirapine (NVP)	Phenytoin	Phenytoin induces the CYP450 system .Reduced drug levels of NVP may occur.	●CSI	Concurrent use of the medication should be avoided if possible
Nevirapine (NVP)	Carbamazepine	Carbamazepine induces the CYP450 system .Reduced drug levels of NVP may occur.	●CSI	Concurrent use of the medication should be avoided if possible
Nevirapine (NVP)	Phenobarbital	induces the CYP450 system .Reduced drug levels of NVP	●CSI	Concurrent use of the medication should be avoided if possible
Nevirapine (NVP)	Indinavir	The indinavir and nevirapine have an antagonistic effect on the CYP3A4 system.	●PCS	Consult experts before considering the options below: Increase indinavir dosage to 1000mg every eight hours
Nevirapine (NVP)	Amprenavir	The amprenavir and NVP have an antagonistic effect on affect the CYP3A4 system. Amprenavir's levels may be reduced	●PCS	Standard dose for NVP; Increase amprenavir dosage to 1,200mg TID
Nevirapine (NVP)	Atazanavir	Probable drug interactions may occur although no data is available	●PCS	Dosages have not yet been established with NVP
Nevirapine (NVP)	Sir John's wort	Induction of CYP450 3A4 by St. John's Wort	●CSI	Avoid concurrent administration
Nevirapine (NVP)	Warfarin	Possibly decreased warfarin effects (e.g., altered INR, increased risk of clotting)	●PCS	Monitor INR or PT and adjust warfarin's dosage accordingly

Nevirapine (NVP)	Ketoconazole	Induction of CYP450 3A4 by nevirapine. Ketoconazole AUC: decreased 63%; Cmax: decreased 40%. Decreased ketoconazole effects	●CSI	Avoid concurrent administration
Nevirapine (NVP)	Cimetidine	Inhibition of CYP450 3A4 by cimetidine.	●NCS	No dose adjustment necessary
Nevirapine (NVP)	Clarithromycin	Nevirapine Cmin: no significant change. Clarithromycin AUC: decreased 29%; Cmax: decreased 20%; Cmin: decreased 46%; 14-hydroxy clarithromycin AUC: increased 27%	●NCS	No dose adjustment necessary
Nevirapine (NVP)	Ethinyl estradiol	Induction of CYP450 3A4 by nevirapine. Ethinyl estradiol: AUC decreased 23%; half-life: decreased 44%; Norethindrone: AUC decreased 18%; half-life: decreased 15%. Possible contraceptive failure	●CSI	Avoid co-administration; additional contraceptive measures may be needed
Ritonavir/lopinavir	Efavirenz	Efavirenz is a potent inducer of the CYP3A4 system. Significant reductions in ritonavir levels may occur when using these two drugs concurrently. The AUC is reduced by about 15%.	●PCS	Consult experts before considering the following option. Ritonavir/lopinavir dosage may need to be increased
Ritonavir/lopinavir	Nevirapine	NVP is a potent inducer of the CYP3A4 system. Significant reductions in ritonavir levels may occur when using these two drugs concurrently. The AUC is reduced by about 33%.	●PCS	Consult experts before considering the following option. Ritonavir/lopinavir dosage need to be increased.
Ritonavir	Alprazolam , midazolam, triazolam	Ritonavir inhibits the CYP3A4 system that metabolises the benzodiazepams. Potential for prolonged or increased sedation or respiratory depression	●CSI	Avoid concurrent use. Substitute with zolpidem ,oxazepam, temazepam or lorazepam
Ritonavir	Simvastatin, lovastatin, high dose atorvastatin	Ritonavir inhibits the CYP3A4 enzymes responsible for the extensive metabolism of the statins. Statins' levels are markedly increased. Risk of toxicity is increased i.e. myopathy, renal failure and even death	●PCS	Use pravastatin or fluvastatin instead as they have minimal effects on CYP450

Ritonavir	Rifampicin	Rifampicin is a potent inducer of CYP3A4, leading to significant reductions in PI levels potentially leading to virologic failure or resistance. May use with full dose ritonavir	●PCS	Consider rifabutin as an alternative
Ritonavir	Amiodarone	Increase in amiodarone levels due to inhibition of CYP450 and CYP3A4 by ritonavir. Increased amiodarone effects	●PCS	Monitor amiodarone levels and decrease its dosage accordingly
Ritonavir	Carbamazepine	Reduction in ritonavir and increase in carbamazepine blood levels	●PCS	Avoid concurrent use. Consider alternative agents for carbamazepine. Monitor carbamazepine levels and adjust dosage accordingly
Ritonavir	Cotrimoxazole	Induction of CYP450 3A4 by ritonavir. Sulfamethoxazole AUC: decreased 20%; trimethoprim AUC: increased 20%	●NCS	No dose adjustment necessary
Ritonavir	Digoxin	Increased digoxin effects	●PCS	Monitor digoxin concentrations closely and adjust dosage accordingly
Ritonavir	Ergotamine	Increased ergotamine effects	●CSI	Do not use concurrently. Replace with 5-HT agonists ("triptans")
Ritonavir	Fluconazole	Inhibition of CYP450 3A4 by fluconazole. Ritonavir Inhibition of CYP450 3A4 by fluconazole	●NCS	No dose adjustment necessary
Ritonavir	Itraconazole	Inhibition of CYP450 3A4 by itraconazole resulting in increased ritonavir effects	●PCS	Dose adjustment not established, consult experts
Ritonavir	Metronidazole	Disulfiram-like reaction (e.g. headache, hypotension, flushing, vomiting) as a reaction with alcohol in the Ritonavir Oral solution	●CSI	Avoid concurrent use
Ritonavir	Phenobarbital	Induction of CYP450 3A4 by Phenobarbital resulting in decreased ritonavir effects	●PCS	Avoid combination if possible; consider alternative agents; monitor phenobarbital levels and adjust accordingly. Possible substitutes are Gabapentin, Lamotrigine, Topiramate
Ritonavir	Sir John's wort	Induction of CYP450 3A4 by St. John's wort resulting in decreased ritonavir effects	●CSI	Avoid concurrent use

Ritonavir	Warfarin	Possible inhibition of CYP450 3A4, 2C9 and 1A2 by ritonavir. Resulting in decreased warfarin effects (e.g., decreased INR, increased risk of clotting)	●PCS	Monitor INR or PT and adjust warfarin's dosage accordingly
Ritonavir	Sildenafil	Inhibition of CYP450 3A4 by ritonavir resulting in Sildenafil increased blood levels and effects such as hypotension, priapism.	●PCS	Consult with experts and initiate therapy at 25 mg dose; do not exceed 25 mg in 48 hour period.
Ritonavir	Phenytoin	Increased phenytoin blood levels and effects.	●CSI	Avoid concurrent use; consider alternative agents such as Gabapentin Lamotrigine Topiramate. Monitor phenytoin levels and adjust its dosage accordingly
Ritonavir	Nifedipine	Inhibition of CYP450 3A4 by ritonavir. Increased nifedipine effects (e.g., hypotension, cardiac arrhythmias)	●PCS	Monitor and adjust nifedipine dosage accordingly
Ritonavir	Fluoxetine	Inhibition of CYP450 2D6 by both drugs. AUC: increased 19%; Cmax: no significant change. Increased ritonavir effects; possibly increased fluoxetine effects	●NCS	No dose adjustment necessary
Ritonavir	Theophylline	Possible induction of CYP450 1A2 by ritonavir. Theophylline AUC: decreased 43%; Cmax: decreased 32%; Cmin: decreased 57%; half-life: decreased 57%	●PCS	Monitor and adjust theophylline as indicated
Ritonavir	Amitriptyline	Inhibition of CYP450 3A4 and 2D6 by ritonavir. Increased amitriptyline effects (e.g., dry mouth, hypotension, confusion). Increased amitriptyline levels.	●PCS	Monitor and adjust amitriptyline dosage accordingly
Ritonavir	Clarithromycin	Inhibition of CYP450 3A4 by ritonavir. Clarithromycin AUC: increased 77%; Cmax: increased 31%; Cmin: increased 182%. Increased clarithromycin effects	●NCS	No dose adjustment necessary

Saquinavir	Alprazolam, midazolam, triazolam	Saquinavir inhibits the CYP3A4 system that metabolises the benzodiazepams. There is a potential for prolonged or increased sedation or respiratory depression. It's the least potent protease inhibitor on the CYP3A4 isoenzyme.	●CSI	Avoid concurrent use. Consider substitution with zolpidem, oxazepam, temazepam or lorazepam
Saquinavir	Simvastatin, lovastatin, high dose atorvastatin	Saquinavir inhibits the CYP3A4 enzymes responsible for the extensive metabolism of the statins. Statins' levels are markedly increased. Risk of toxicity is increased i.e. myopathy, renal failure and even death	●PCS	Select pravastatin or fluvastatin as they have minimal effects on CYP450 or use low dose of atorvastatin with close follow-up for potential hepatotoxicity
Saquinavir	Rifampicin	Rifampicin is a potent inducer of CYP3A4 and CYP450, leading to significant reductions in saquinavir levels potentially leading to virologic failure or resistance. AUC: decreased 84%; Cmax: decreased 79%	●CSI	Consider rifabutin as an alternative. Avoid if possible; may consider saquinavir 400 mg BID with ritonavir 400 mg BID
Saquinavir	Garlic	Garlic induces the CYP3A4 enzymes resulting in significant decrease in saquinavir levels. Potential virologic failure or resistance	●CSI	Avoid concurrent use particularly when Saquinavir is the sole PI in the regimen
Saquinavir	Carbamazepine	Induction of CYP450 and CYP3A4 by carbamazepine may reduce saquinavir levels	●PCS	Avoid concurrent use; consider alternative agents; monitor carbamazepine levels and adjust dosage accordingly
Saquinavir	Fluconazole	Inhibition of CYP450 3A4 by fluconazole. Saquinavir AUC: increased 50%; Cmax: increased 56%.	●PCS	Dosage adjustments necessary
Saquinavir	Itraconazole	Inhibition of CYP450 3A4 by itraconazole.	●NCS	No dose adjustment necessary
Saquinavir	Phenobarbital	Induction of CYP450 3A4 by Phenobarbital. May decrease saquinavir effects.	●CSI	Avoid combination if possible; consider alternative agents; monitor phenobarbital levels and adjust dosage accordingly. Suggested alternatives are: Gabapentin, Lamotrigine
Saquinavir	Sir John's wort	Possible induction of CYP450 3A4 by St John's Wort resulting in decreased saquinavir effects.	●CSI	Avoid concurrent use

Saquinavir	Warfarin	Possible inhibition of CYP450 by saquinavir. Increased warfarin effects (e.g., increased INR and risk of bleeding)	●PCS	Monitor INR or PT and adjust warfarin as indicated
Saquinavir	Sildenafil	Inhibition of CYP450 3A4 by saquinavir. Sildenafil AUC: increased 200-1100%. Increased sildenafil effects (e.g., headache, flushing, priapism)	●PCS	Initiate sildenafil at 25 mg daily; adjust dose as indicated; not recommended to exceed 25 mg in a 48-hours period
Saquinavir	Ranitidine	Inhibition of CYP450 3A4 by ranitidine. Saquinavir AUC: increased 67%; Cmax: increased 74%.	●NCS	No dose adjustment necessary
Saquinavir	Phenytoin	Induction of CYP450 3A4 by phenytoin. May decrease saquinavir levels	●CSI	Avoid combination if possible; consider alternative agents; monitor phenytoin levels and adjust as indicated. Suggested Alternative Agent(s): Gabapentin, Lamotrigine, Tiagabine, Topiramate
Saquinavir	Ketoconazole	Inhibition of CYP450 3A4 by ketoconazole. Increased saquinavir effects	●PCS	Dose adjustment not established
Saquinavir	Grape fruit	Inhibition of gastrointestinal CYP450 3A4 by grapefruit juice. Saquinavir AUC: increased 50%; increased saquinavir effects	●PCS	Separate grapefruit juice from saquinavir administration by at least 2 hours
Saquinavir	Clarithromycin	Inhibition of CYP450 3A4 by clarithromycin. Clarithromycin AUC: increased by 45%	●PCS	Dose adjustment not established
Saquinavir	Dexamethasone	Possible induction of CYP450 3A4 by dexamethasone. May decrease saquinavir levels	●NCS	No dose adjustment necessary
Saquinavir	Erythromycin	Inhibition of CYP450 3A4 by erythromycin. Increased saquinavir effects	●PCS	Dose adjustment not established
Stavudine	Zidovudine	Competitive inhibition of intracellular phosphorylation of stavudine, with decreased stavudine effects	●CSI	Avoid concurrent use
Stavudine	Didanosine	Cmax increased by 17%	●NCS	No dose adjustment necessary

Stavudine	Ethambutol	Concurrent use increases risk of neuropathy	●CSI	Avoid concurrent use
Stavudine	Ethionamide	Concurrent use increases risk of neuropathy	●CSI	Avoid concurrent use
Stavudine	Isoniazid	Concurrent use increases risk of neuropathy	●CSI	Avoid concurrent use
Stavudine	Dapsone	Concurrent use increases risk of neuropathy	●CSI	Avoid concurrent use
Stavudine	Zalcitabine	Concurrent use increases risk of neuropathy	●CSI	Avoid concurrent use
Zidovudine	Stavudine	The thymidine analogues both compete for the same phosphorylation sites in the growing chain of HIV DNA	●CSI	Avoid concurrent use
Zidovudine	Fluconazole	Zidovudine AUC: increased by 74%; Half-life: increased by 128%. Increased zidovudine effects.	●NCS	No dose adjustment necessary
Zidovudine	Rifampicin	Avoid if possible; may consider saquinavir 400 mg BID with ritonavir 400 mg BID	●NCS	No dose adjustment necessary
Zidovudine	Valproic acid	Inhibition of glucuronidation of Zidovudine, AUC: increased by 79%, and increased effects	●NCS	No dose adjustment necessary
Zidovudine	Phenytoin	Zidovudine clearance: decreased by 30%	●NCS	No dose adjustment necessary
Zidovudine	Clarithromycin	Zidovudine Cmax: increased by 50%; AUC: no significant change	●NCS	No dose adjustment necessary
Zidovudine/ Lamivudine	Stavudine	The thymidine analogues both compete for the same phosphorylation sites in the growing chain of HIV DNA	●CSI	Avoid concurrent use
Zidovudine/ Lamivudine	Valproic acid	Zidovudine AUC: increased by 100% with increased effects	●NCS	No dosage adjustment necessary
Zidovudine/ Lamivudine	Ganciclovir	Zidovudine AUC: increased by 19.5%; Cmax: increased by 62% with increased effects	●PCS	Avoid combination if possible and monitor and adjust dosage accordingly
Zidovudine/ Lamivudine	Cotrimoxazole	Lamivudine AUC: increased by 44% and increased effects	●NCS	No dose adjustment necessary

Legend:

- Green=NCS => no clinically significant interaction, no action required
- Blue =PCS => potentially clinically significant interaction, require close monitoring, dose or and timing adjustment as indicated
- Red =CSI => clinically significant interaction, these drugs should not be administered concurrently or concomitantly.

### 3.2. Drug-Food Interactions

Food intake or meals can enhance or inhibit the absorption, metabolism, distribution and excretion of drugs. Dietary management to improve the efficacy of a drug includes taking it with food, on an empty stomach, taking it with particular foods or avoiding particular foods.

<i>Drug</i>	<i>Food Restriction</i>	<i>Other nutrient restrictions</i>
Efavirenz	Take on an empty stomach, food seems to increase absorption	Avoid alcohol
Nevirapine	Not affected by food. Take without regard to meals.	
Stavudine	Give without regard to meals	
Lamivudine	Take without regard to meals (though may delay absorption)	
Didanosine	Take on an empty stomach, 1hr before a meal or 2hrs after.	Buffered tablets can be dispersed in clear apple juice
Zidovudine	Take with low fat meal	
Lopinavir/ritonavir	Food significantly increases plasma concentration. Take with meals.	

### 3.3. Herb/Traditional/Complementary-Drug Interactions

According to the National comprehensive treatment plan in South Africa, about 90% of HIV +ve patients take some complementary or herbal medicine. This implies that a majority of patients on ARTs will also be taking some form of herbal, traditional or complementary medicine. Research on herbal or traditional medicines is very limited and thus have not been regulated for purity and potency. There is inadequate clinician experience combining herbal, traditional or complementary medicines with ARVs. It is however prudent that clinicians should document as much as possible the name, source and quantity of any other medicines that the patient is taking. Clinicians should counsel patients on the possibility of drug interactions that may result to therapeutic failure or toxicities.

The following complementary medicines have however been documented to have an effect on the cytochrome p450 enzyme system:

- St. John's wort
- Garlic
- Ginseng
- Melatonin
- Milk thistle
- Geniposide
- Scullcap

## Bibliography and Additional Information

For more information on Drug Interactions consult the following:

### 1. Websites:

- [hivinsite.ucsf.edu](http://hivinsite.ucsf.edu)
- [www.hiv-druginteractions.org](http://www.hiv-druginteractions.org)
- [www.tthivclinic.com](http://www.tthivclinic.com)
- [www.aids-etc.org](http://www.aids-etc.org)
- [www.rx.com](http://www.rx.com)
- [www.unaids.org](http://www.unaids.org)
- [www.medadvocates.org/marg/children/HIVTreatmentGuidelines/](http://www.medadvocates.org/marg/children/HIVTreatmentGuidelines/)
- 

### 2. Books

- South African Medicine Formulary. 6<sup>th</sup> Edition.
- National Antiretroviral Treatment Guidelines. 2004

### 3. Package inserts of registered ARV drugs