

INTRODUCTION

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.

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 programmes, 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.

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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:.....

Figure 1:

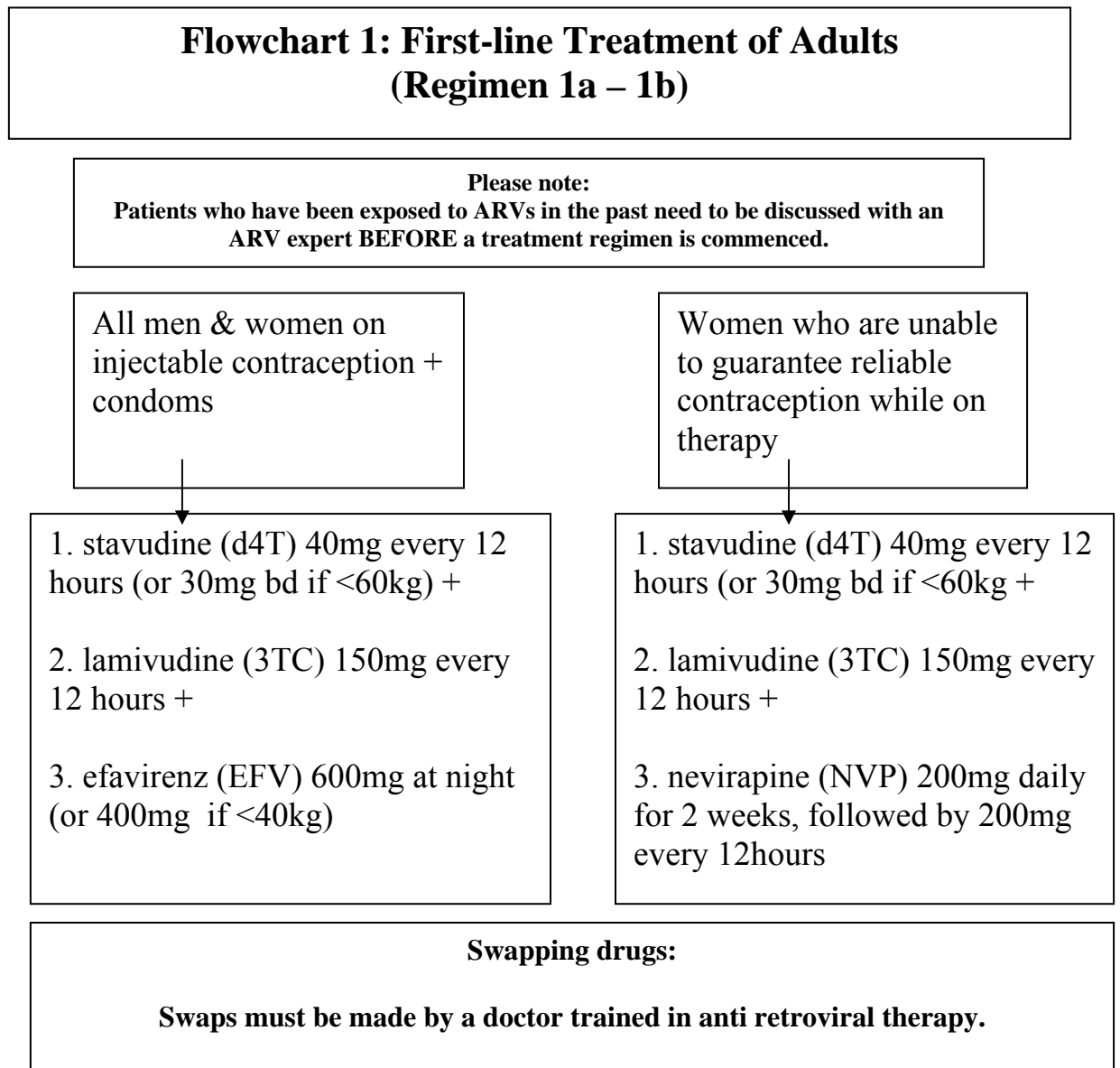


Figure 2:

Second-line antiretroviral therapy in adults (Regimen 2)

1. zidovudine (AZT) 300mg every 12 hours, with
2. didanosine (ddI) 400mg once a day (250mg daily if <60kg), taken alone, dissolved in water on an empty stomach, and
3. lopinavir/ritonavir (LPV/r) 400/100mg every 12 hours

Patients need to keep their lopinavir/ritonavir safe, cool & dry (<25°C)

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 (ddI) + Zidovudine (ZDV) + Nevirapine
>3yrs old and > 10kg	Didanosine (ddI) + Zidovudine (ZDV)+ Lopinavir/Ritonavir

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

Table 3: Paediatric dosages per body surface area

Body surface (m ²)	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

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-Central Nervous System 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 4th week, but can persist as mild symptoms for a longer time. These CNS effects can be aggravated by psychoactive drugs or alcohol.

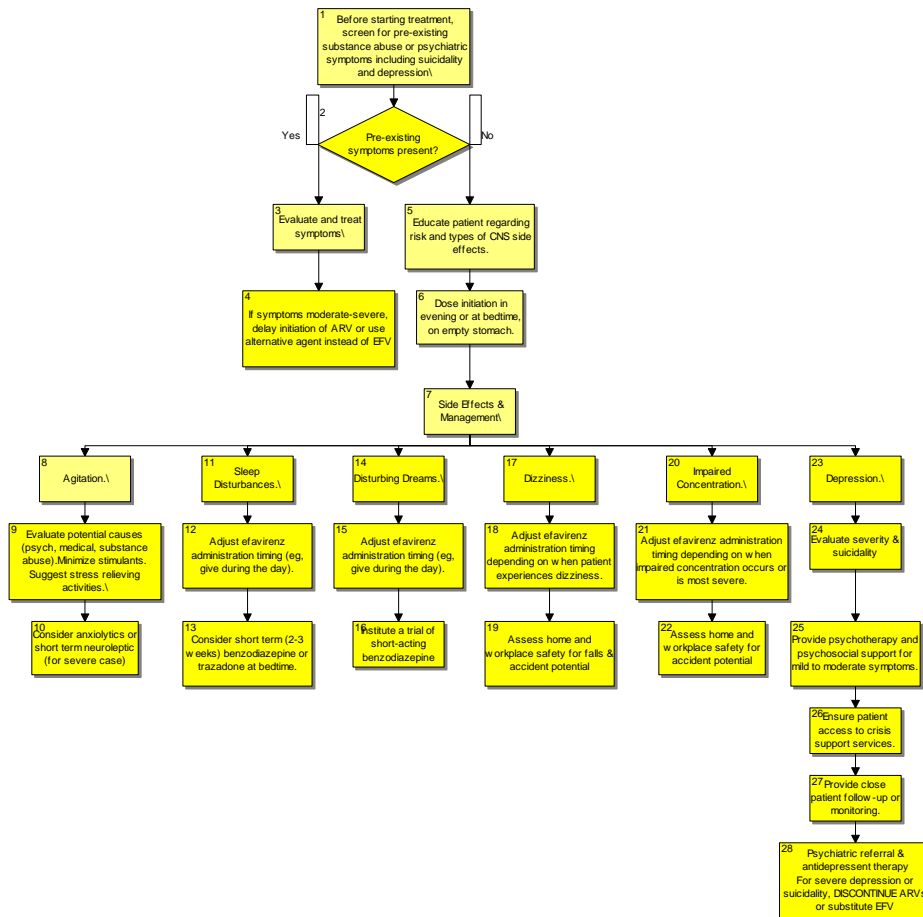
According to Barlett et al, the recommended paradigm for initiating treatment with Efavirenz is:

- **Prepare:** Screen and stabilize preexisting neuropsychiatric (NP) symptoms
- **Educate:** Regarding most common NP side effects
- **Reassure:**
 - Efavirenz is effective for HIV
 - NP side effects are in the mild-to-moderate range and time limited
 - NP side effects result in few discontinuations
- **Treat:** Address new-onset and persistent NP symptoms

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.*

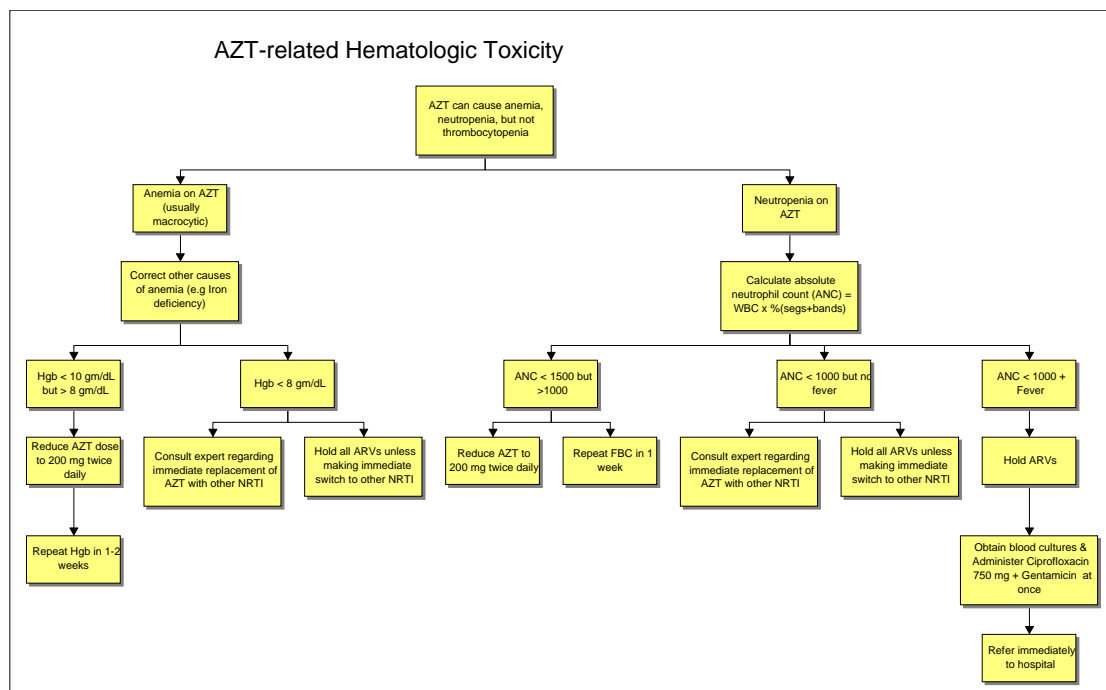
Management of Efavirenz-related CNS Side Effects
(adapted from: Canadian J of Infect Dis: July/August 2001, Volume 12, Number C)



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.

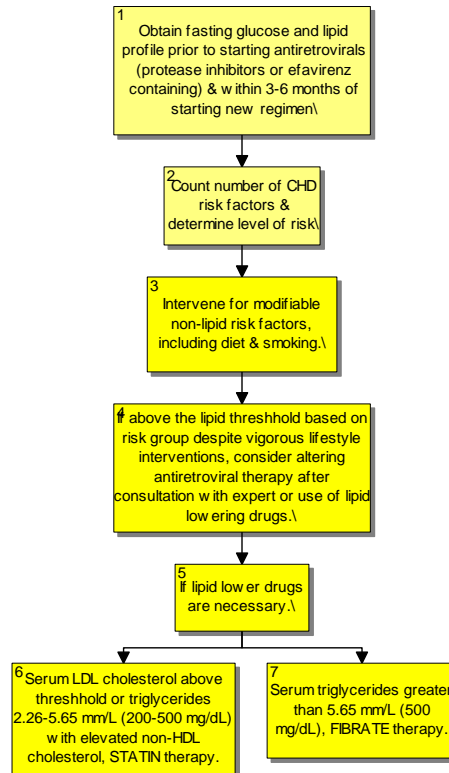


2.3. Dyslipidemia (Lipid Abnormalities)

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)

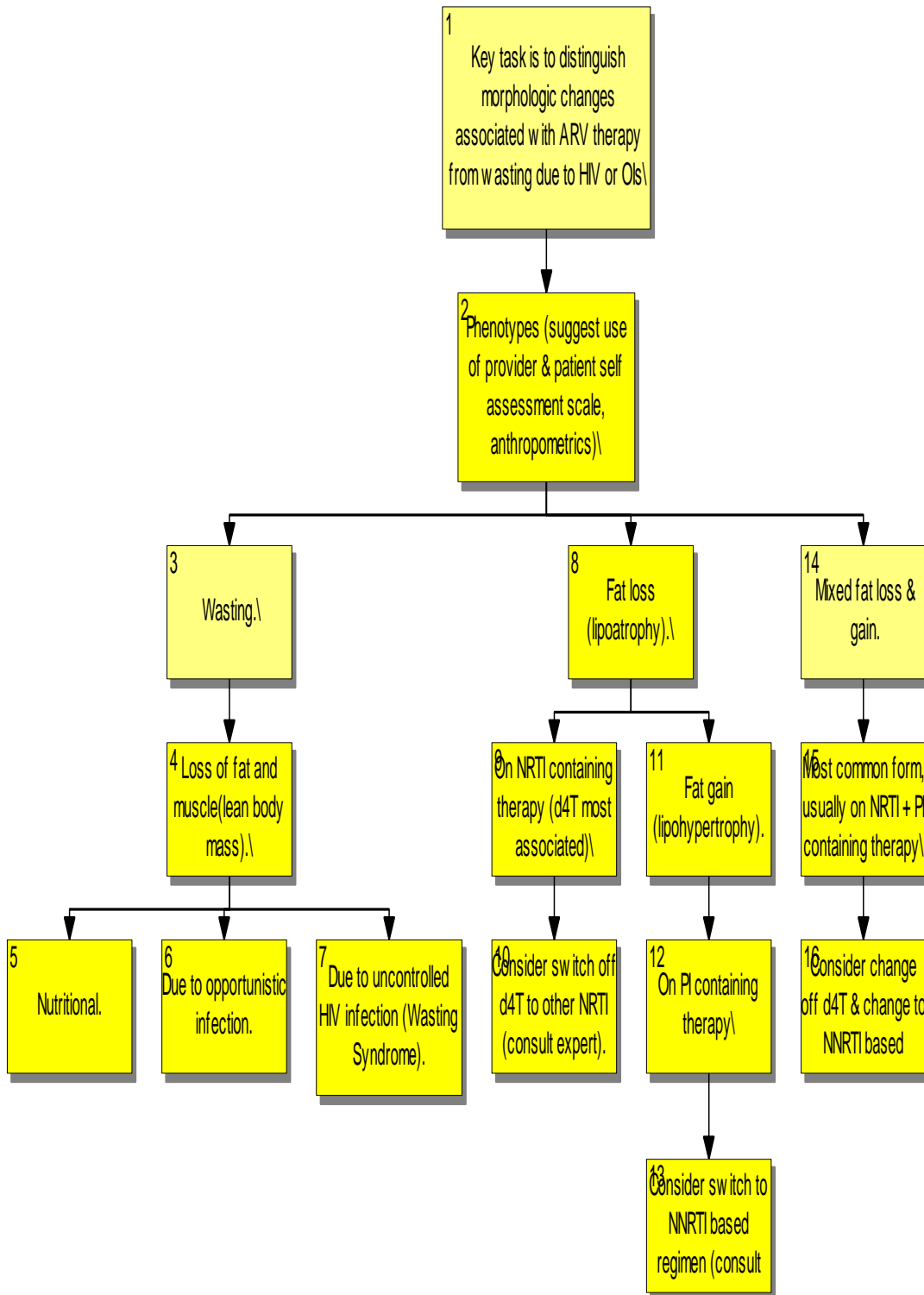


2.4. Lipodystrophy

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

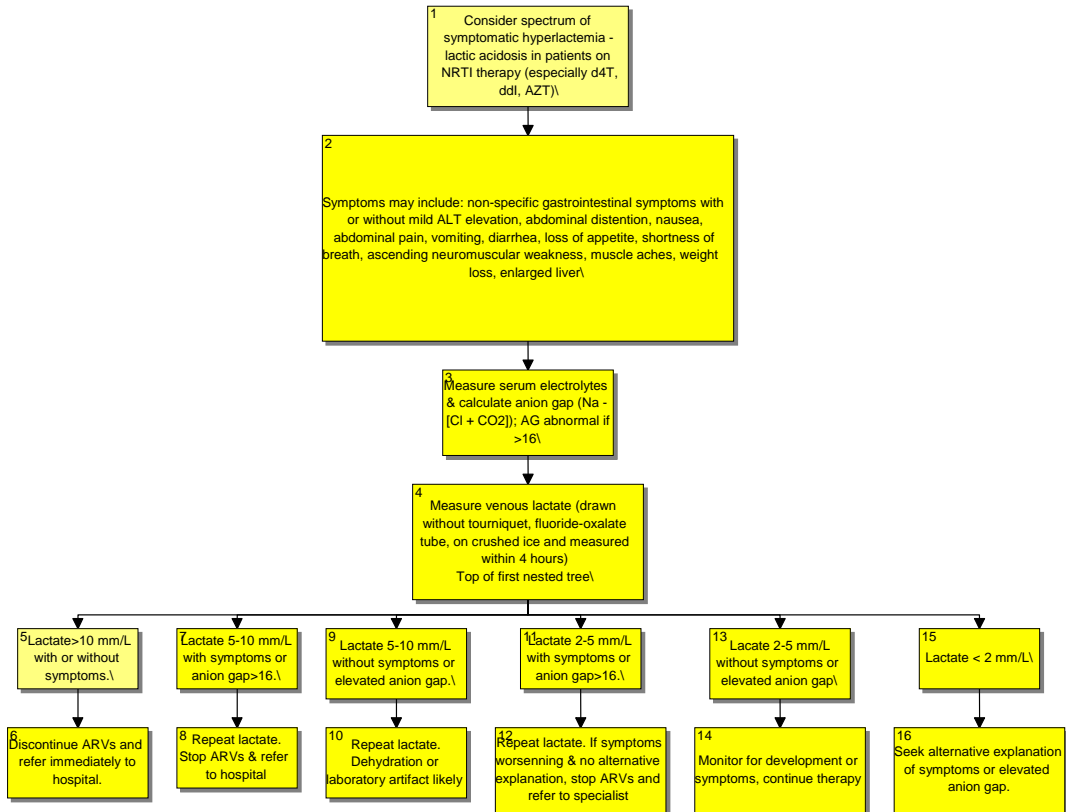


2.5. Lactic Acidosis

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.

Management of Lactic Acidemia

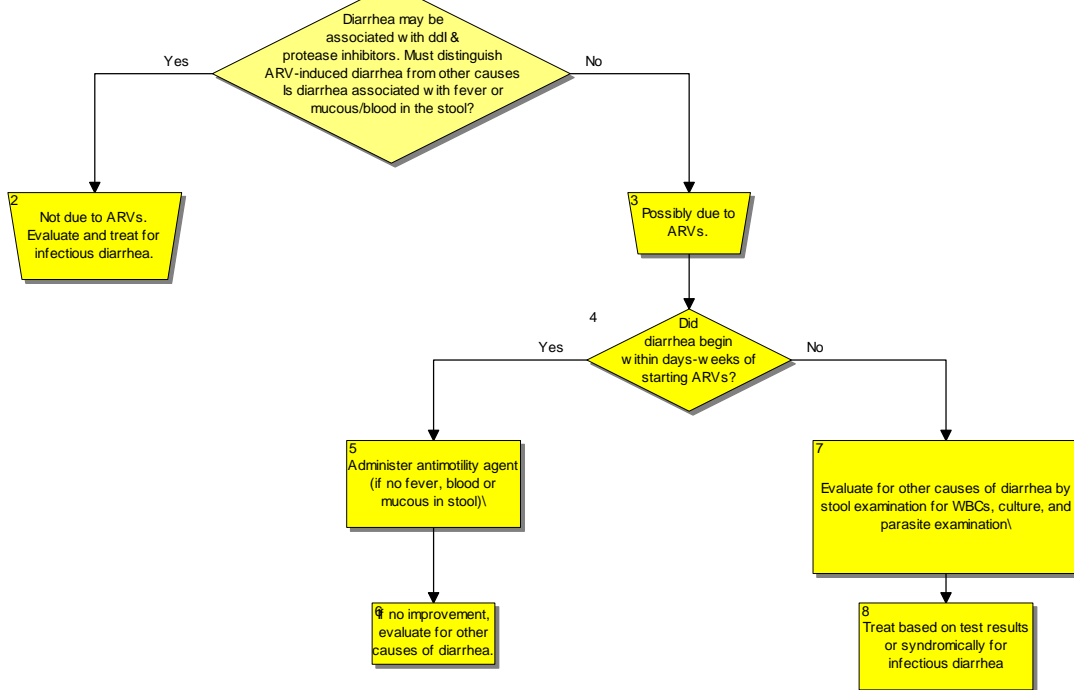
(Adapted from Carr, A., Clinical Infectious Diseases 2003; 36(Suppl 2):S96–100)



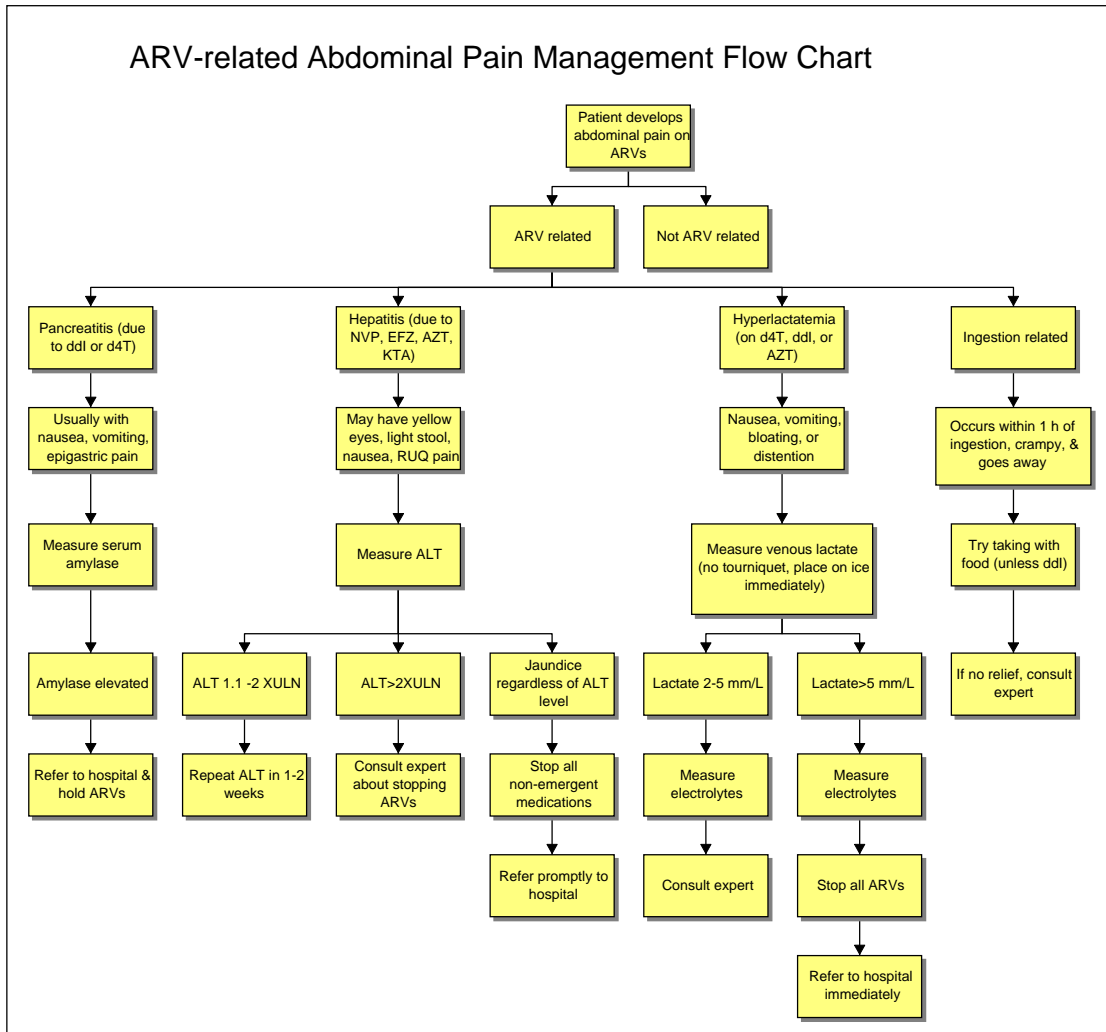
2.6. Gastrointestinal side effects

Abdominal discomforts are the most commonly reported side effects with ARVs and may occur earlier on in therapy. Common patient complaints 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.

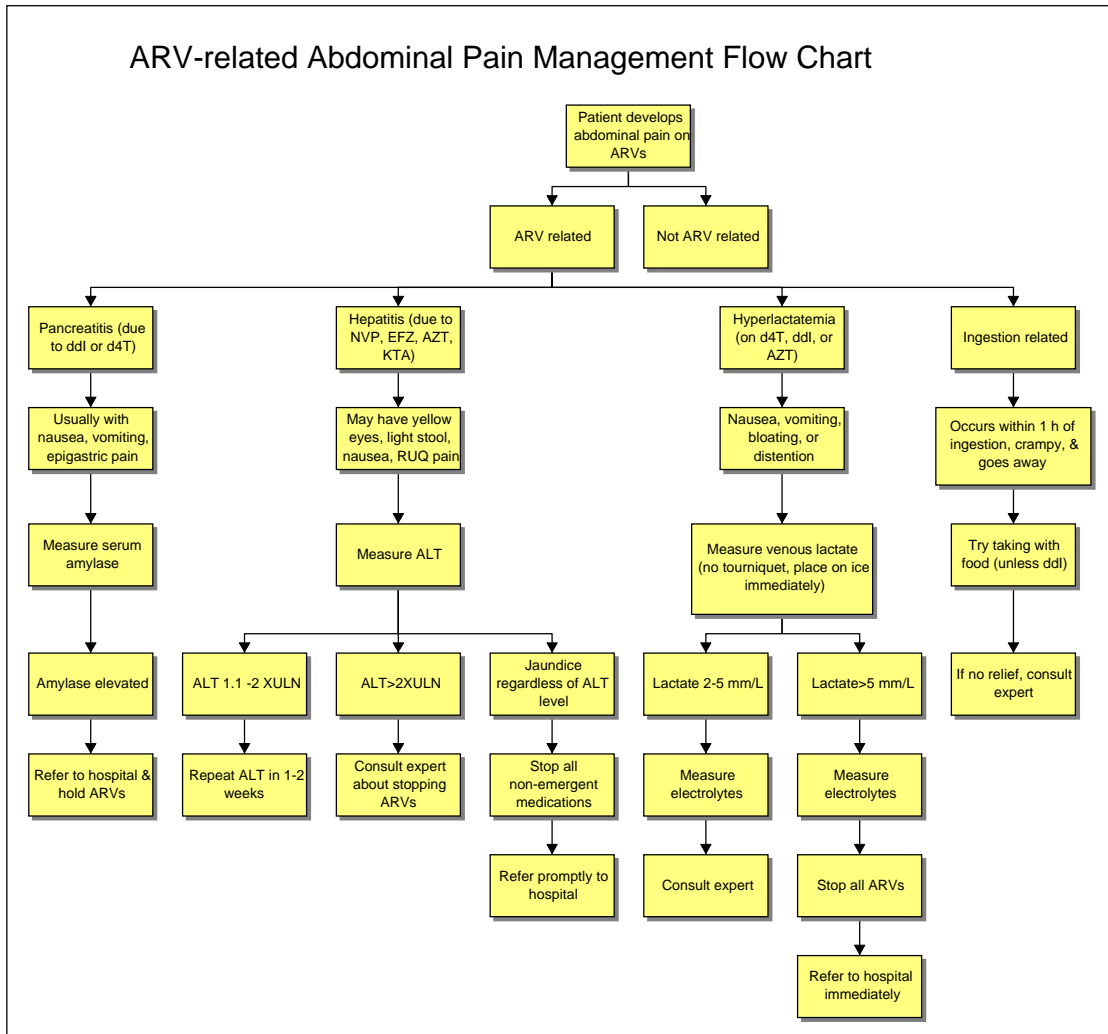
ARV-associated Diarrhea Management



ARV-related Abdominal Pain Management Flow Chart



ARV-related Abdominal Pain Management Flow Chart

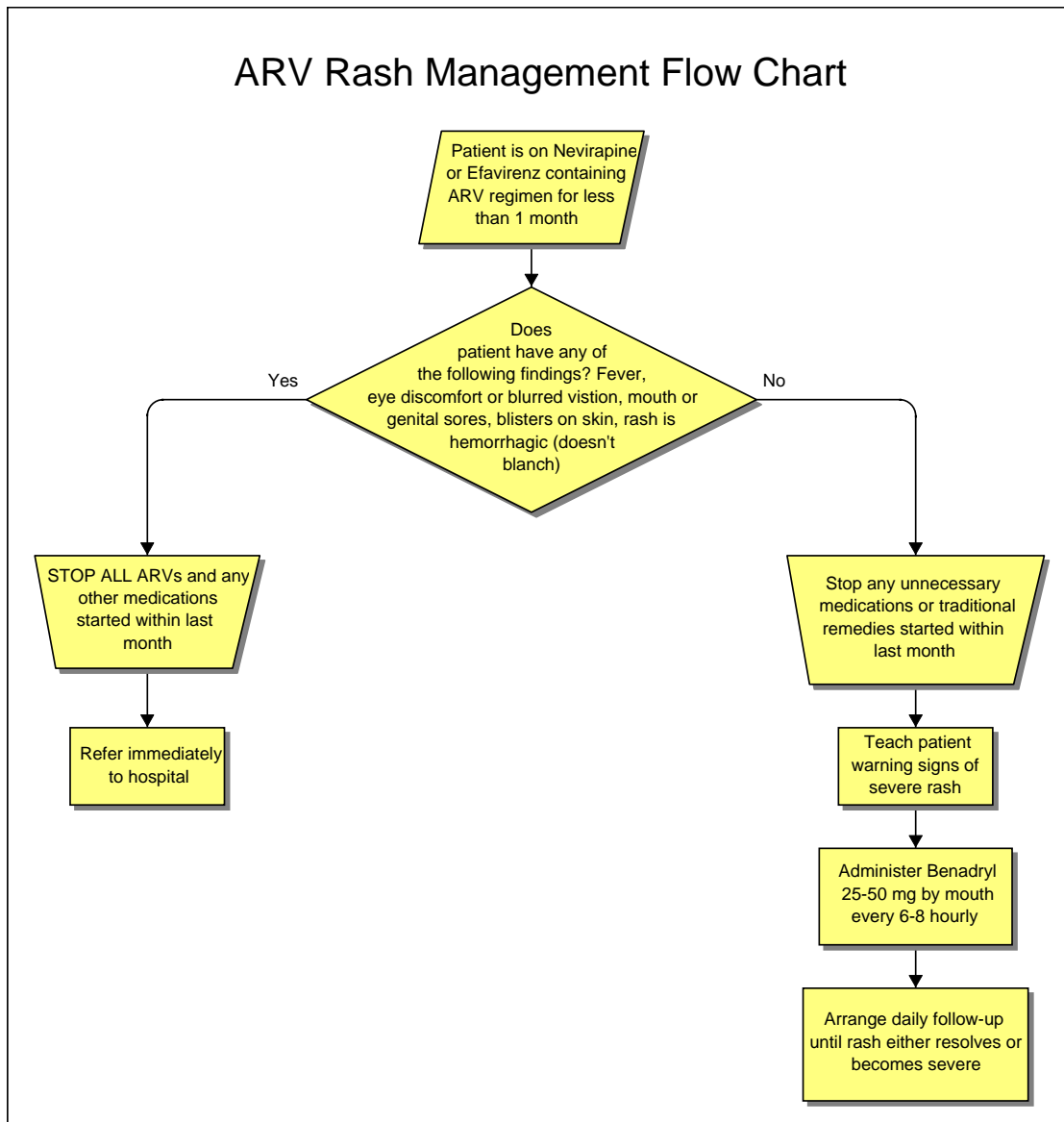


2.7. Allergies

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.

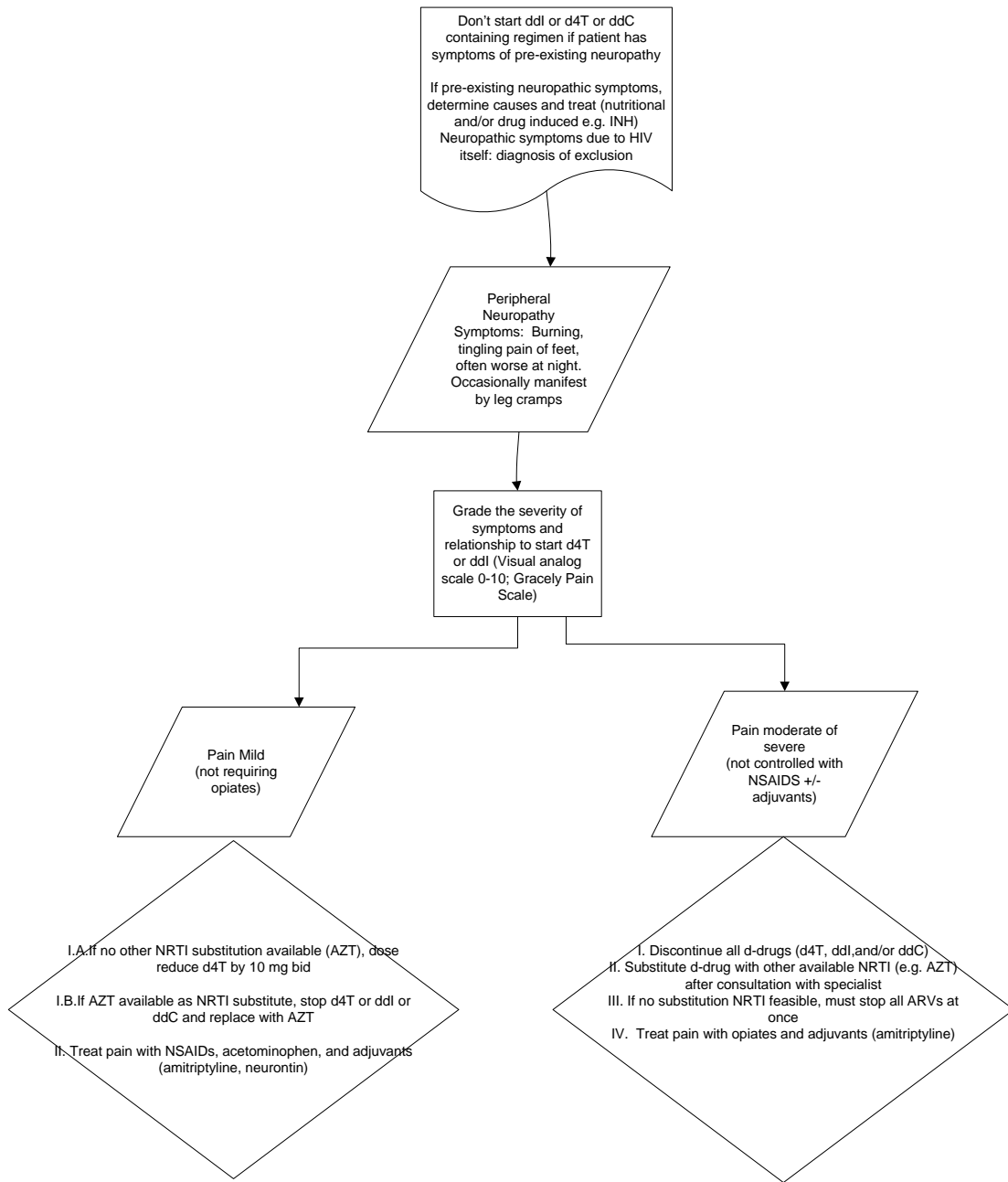
Abacavir causes a hypersensitivity reaction (HSR) in 5-10% of patients which can be fatal. HSR is not dose dependent and usually involves multiorgan systems. Abacavir HSR is characterized by fever and usually accompanied by general malaise, nausea, vomiting, diarrhea and abdominal. Rash may occur but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

ARV Rash Management Flow Chart



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 pharmacologic response (drug effect) of a second without a resultant change in drug

concentrations or pharmacokinetic parameters. In this type of interaction, the pharmacologic response from the drug can be antagonistic, additive, or synergistic.

- Antagonistic effects result in the drug's pharmacologic 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 pharmacologic 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)

<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

Drug Name	Interacting drug	Effect of interaction	Clinical significance	Management
Abacavir	Alcohol	Decreased abacavir metabolism by alcohol dehydrogenase. Abacavir AUC: increased 41%; half-life: increased 26%	●	No dose adjustment necessary
	Zidovudine	Abacavir decreases the absorption of zidovudine. Reduced C _{max}	●	No dose adjustment necessary

	Lamivudine	Abacavir decreases the absorption of lamivudine. Reduced Cmax	●	No dose adjustment necessary
Indinavir	Efavirenz	Efavirenz is a potent inducer of the CYP3A4 system. Significant reductions in Indinavir levels may occur when using these two drugs concurrently. The AUC is reduced by about 33%	●	Increase the does of indinavir to 1000 mg every eight hours
	Delavirdine	Delavirdine is a potent inhibitor of CYP3A4. It therefore leads to an increase in indinavir levels	●	Indinavir requires a dosage reduction to 600mg every eight hours
	Nevirapine	NVP is a potent inducer of the CYP3A4 system. Significant reductions in Indinavir levels may occur when using these two drugs concurrently. The AUC is reduced by about 33%	●	Increase the dosage of indinavir to 1000 mg every eight hours

Alprazolam, midazolam, triazolam	Indinavir inhibits the CYP3A4 system that metabolizes the benzodiazepams. Potential for prolonged or increased sedation or respiratory depression.	●	Avoid concurrent use. Consider substitution: zolpidem, temazepam, lorazepam
Simvastatin, lovastatin, high dose atorvastatin	Indinavir 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	●	Avoid concurrent use. Use instead pravastatin or fluvastatin as they have minimal effects on CYP450; or low dose artovastatin with close follow-up for potential hepatotoxicity
Isoniazid	No significant change in blood levels of both drugs	●	No dose adjustment necessary

Rifampin	Induction of CYP450 3A4 by rifampin; inhibition of CYP450 3A4 by indinavir/ritonavir .Significant reductions in indinavir levels potentially leading to virologic failure or resistance. Indinavir AUC: decreased 81%. Rifampin AUC: increased 25%, with increased effects	●	Avoid concurrent use. Consider rifabutin as an alternative
St.John's wort	St. John's wort induces the CYP3A4 enzymes resulting in significant decrease in indinavir levels. Potential virologic failure and resistance	●	Avoid concurrent use.
Amiodarone	Amiodarone increased by 44% due to inhibition of CYP450 and CYP3A4 by indinavir	●	Monitor and adjust amiodarone as indicated. Dose reductions may be necessary

Carbamazepine	Induction of CYP3A4 and CYP450 by carbamazepine. Indinavir levels decreased by 4 to 25% of mean population values	●	Avoid concurrent use. Consider alternatives to carbamazepine, monitor its levels. Adjust Indinavir dosage accordingly
Cotrimoxazole	Trimethoprim AUC: increased by 19%; but no change of sulfamethoxazole AUC	●	No dose adjustment necessary
Ergotamine	Inhibition of CYP450 3A4 by indinavir. Increased ergotamine effects (ergotism)	●	Avoid concurrent use. Substitute with 5-HT agonists (“triptans”)
Fluconazole	Indinavir AUC: decreased by 19-24%; Cmax and Cmin: no significant change	●	No dose adjustment necessary
Itraconazole	Inhibition of CYP450 3A4 by itraconazole. Increased indinavir effects	●	Decrease indinavir to 600 mg Q8H

Omeprazole	Decreased gastric acidity may affect indinavir solubility and absorption. Indinavir AUC: decreased by 25%	●	No dose adjustment necessary
Prednisone	Indinavir AUC: increased 38%. Increased indinavir effects	●	No dose adjustment necessary
Sir John's wort	Possible induction of CYP450 3A4 by St. John's wort. Indinavir AUC: decrease 57+/- 19%.	●	Avoid concurrent use. Note that active ingredients or quantity of <i>Hypericum sp</i> varies between products and among individual tablets or capsules of the same product
Vitamin C	Indinavir AUC: no significant change; Cmin: decreased by 32%; Cmax by 20%	●	No dose adjustment necessary

Warfarin	Inhibition of CYP450 by indinavir. Prothrombin complex activity increased from 25-35% to 53 and 43% at 10 and 25 days after indinavir discontinued in one patient. Increased warfarin effects (egg, increased INR, risk of bleeding)	•	Monitor INR and adjust warfarin dosage based on INR readings
Sildenafil	Inhibition of CYP450 3A4 by indinavir. Sildenafil AUC and Cmax increased by 300% (exceeding those achieved by a 100 mg single dose), increased effects (priapism, hypotension)	•	Initiate sildenafil at 25 mg daily; do not exceed 25 mg in a 48-hours period!
Phenytoin	Induction of CYP450 3A4 by phenytoin. Decreased effects of indinavir	•	Avoid combination, or monitor phenytoin's levels. Or Use alternative agents such as Gabapentine

Orange juice	Inhibition of intestinal CYP450 3A4 by Seville orange juice or grapefruit juice was not observed in this study.	●	May consider decreasing indinavir to 600 mg Q8H
Ketoconazole	Inhibition of CYP450 3A4 by ketoconazole. Increased indinavir effects. Indinavir AUC: increased 68%	●	No dose adjustment necessary
Grape fruit juice	Inhibition of CYP450 3A4 by Seville orange juice or grapefruit juice was not observed in this study. Increased gastric acidity reduced indinavir absorption	●	No dose adjustment necessary. Consider separating grapefruit juice and indinavir by at least 2 hours
Theophylline	Inhibition of P450 3A4 by indinavir. Theophylline AUC: increased 18%; theophylline Cmax: within 8% of that when given alone	●	No dose adjustment necessary
Azithromycin	No significant change in levels of indinavir	●	No dose adjustment Necessary

Cimetidine	No significant change in indinavir drug levels	●	No dose adjustment necessary
Clarithromycin	Inhibition of CYP450 3A4 by both drugs. Clarithromycin AUC: increased 53%. Indinavir AUC: increased by 29%	●	No dose adjustment necessary
Dexamethasone	Induction of CYP450 3A4 by dexamethasone. May decrease indinavir levels	●	No dose adjustment necessary
Ethinyl estradiol	Ethinyl estradiol AUC: increased 24%; norethindrone AUC: increased 26%	●	No dose adjustment necessary
Cisapride	Increase in cisapride levels	●	Do not administer concurrently

Ritonavir	Efavirenz	Efavirenz is a potent inducer of the CYP3A4 system. Significant reductions in ritonavir levels, AUC is reduced by about 33%	●	The dosage for Lopinavir/ritonavir combination needs to be increased to 533mg /133mg twice daily
	Nevirapine	NVP is a potent inducer of the CYP3A4 system. Significant reductions in ritonavir levels AUC is reduced by about 33%.	●	The dosage for Lopinavir/ritonavir combination needs to be increased to 533mg /133mg twice daily
	Alprazolam , midazolam, triazolam	Ritonavir inhibits the CYP3A4 system that metabolises the benzodiazepams. Potential for prolonged or increased sedation or respiratory depression	●	Avoid concurrent use. Substitute with zolpidem ,oxazepam, temazepam or lorazepam

	Simvastatin, lovastatin, high dose atorvastatin	Ritonavir inhibits the CYP3A4 enzymes responsible for the extensive metabolism of the statins. Statin levels are markedly increased. Risk of toxicity is increased i.e. myopathy, renal failure and even death	•	Use pravastatin or fluvastatin instead as they have minimal effects on CYP450
	Rifampin	Rifampin is a potent inducer of CYP3A4, leading to significant reductions in ritonavir levels potentially leading to virologic failure or resistance.	•	Consider rifabutin as an alternative
	Amiodarone	Increase in amiodarone levels due to inhibition of CYP450 and CYP3A4 by ritonavir; with increased effects	•	Monitor amiodarone levels and decrease its dosage accordingly
	Carbamazepine	Reduction in ritonavir and increase in carbamazepine blood levels	•	Avoid concurrent use. Monitor levels carbamazepine; use alternatives

	Cotrimoxazole	Induction of CYP450 3A4 by ritonavir. Sulfamethoxazole AUC: decreased 20%; trimethoprim AUC: increased 20%	●	No dose adjustment necessary
	Digoxin	Increased digoxin effects	●	Monitor digoxin concentrations closely and adjust dosage accordingly
	Ergotamine	Increased ergotamine effects	●	Do not administer concurrently. Replace with 5-HT agonists ("triptans")
	Fluconazole	Inhibition of CYP450 3A4 by fluconazole. Ritonavir Inhibition of CYP450 3A4 by fluconazole	●	No dose adjustment necessary
	Itraconazole	Inhibition of CYP450 3A4 by itraconazole. Increased ritonavir effects	●	Dose adjustment not established

	Metronidazole	Disulfiram-like reaction (headache, hypotension, flushing, vomiting) as a reaction with alcohol in the Ritonavir Oral solution	●	Do not administer concurrently
	Phenobarbital	Induction of CYP450 3A4 by Phenobarbital. Decreased ritonavir effects	●	Avoid combination if possible; consider alternative agents such as Lamotrigine, Topiramate. Or monitor phenobarbital levels and adjust dosage accordingly.
	Sir John's wort	Induction of CYP450 3A4 by St. John's wort. Decreased ritonavir effects	●	Do not administer concurrently
	Warfarin	Possible inhibition of CYP450 3A4, 2C9 and 1A2 by ritonavir. Decreased warfarin effects (egg, decreased INR, increased risk of clotting)	●	Monitor INR and adjust warfarin as indicated

	Sildenafil	Inhibition of CYP450 3A4 by ritonavir. Sildenafil AUC: increased 1000%; Cmax: increased 290%; Tmax: delayed 3 hours. Increased sildenafil effects (hypotension, priapism)	●	Initiate therapy at 25 mg dose; do not exceed 25 mg in 48-hour period
	Phenytoin	Increased phenytoin levels	●	Avoid combination if possible; consider alternative agents such as Lamotrigine. Monitor phenytoin levels and adjust its dosage accordingly
	Nifedipine	Inhibition of CYP450 3A4 by ritonavir. Increased nifedipine effects (egg, hypotension, cardiac arrhythmias)	●	Monitor and adjust nifedipine dosage accordingly

	Fluoxetine	Inhibition of CYP450 2D6 by both drugs. AUC: increased 19%; Increased ritonavir effects; possibly increased fluoxetine effects	●	No dose adjustment necessary
	Theophylline	Possible induction of CYP450 1A2 by ritonavir. Theophylline AUC: decreased 43%; Cmax: decreased 32%; Cmin: decreased 57%; half-life: decreased 57%	●	Monitor and adjust theophylline as indicated
	Amitriptyline	Inhibition of CYP450 3A4 and 2D6 by ritonavir. Increased amitriptyline effects (egg, dry mouth, hypotension, confusion). Increased amitriptyline levels.	●	Monitor and adjust amitriptyline as indicated

	Clarithromycin	Inhibition of CYP450 3A4 by ritonavir. Clarithromycin AUC: increased 77%; Cmax: increased 31%; Cmin: increased 182%. Increased clarithromycin effects	●	No dose adjustment necessary
Saquinavir	Alprazolam , midazolam, triazolam	Saquinavir inhibits the CYP3A4 system that metabolises benzodiazepams. There is a potential for prolonged or increased sedation or respiratory depression	●	Avoid concurrent use. Consider substitution with temazepam or lorazepam
	Simvastatin, lovastatin, high dose of atorvastatin	Saquinavir inhibits the CYP3A4 enzymes responsible for the extensive metabolism of the statins. Statin levels are markedly increased. Risk of toxicity is increased i.e. myopathy, renal failure and even death	●	Use pravastatin or fluvastatin as they have minimal effects on CYP450. Or a low dose atorvastatin with close follow-up for potential hepatotoxicity

	Rifampin	Rifampin 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%	●	Avoid if possible; Consider rifabutin as an alternative or use saquinavir 400 mg BID
	Garlic	Garlic induces the CYP3A4 enzymes resulting in significant decrease in saquinavir levels, potential virologic failure or resistance	●	Avoid concurrent therapy
	Carbamazepine	Induction of CYP450 and CYP3A4 by carbamazepine may reduce saquinavir levels	●	Avoid concurrent use. Consider alternative agents. Monitor carbamazepine levels and adjust dosage accordingly
	Fluconazole	Inhibition of CYP450 3A4 by fluconazole, leading to 50% increase in AUC	●	Adjust dosage accordingly

		and Cmax of saquinavir		
	Itraconazole	Inhibition of CYP450 3A4 by itraconazole.	●	No dose adjustment necessary
	Garlic	Possible induction of gut mucosal CYP450 3A4 by garlic; P-glycoprotein effects are also possible. Saquinavir AUC: decreased 51%; Cmax: decreased 54%; Cmin: decreased 49% After a 10 day garlic washout period, pharmacokinetic values returned to only 60-70% of baseline.	●	Avoid garlic supplements when saquinavir is used as the sole protease inhibitor
	Phenobarbital	Induction of CYP450 3A4 by Phenobarbital. May decrease saquinavir effects.	●	Avoid combination if possible; consider alternative agents such as Gabapentin. Monitor phenobarbital levels and adjust dosage

	Sir John's wort	Possible induction of CYP450 3A4 by St. John's Wort. Decreased saquinavir effects.	●	Avoid concurrent use. Use alternative antidepressants
	Warfarin	Possible inhibition of CYP450 by saquinavir. Increased warfarin effects (egg, increased INR and risk of bleeding)	●	Monitor INR and adjust warfarin as indicated
	Sildenafil	Inhibition of CYP450 3A4 by saquinavir. Sildenafil AUC: increased by 200-1100%; increased effects (headache, priapism)	●	Initiate sildenafil at 25 mg daily; do not exceed 25 mg in a 48 hour period
	Ranitidine	Inhibition of CYP450 3A4 by ranitidine. Saquinavir AUC: increased 67%, Cmax by 74%	●	No dose adjustment necessary

	Phenytoin	Induction of CYP450 3A4 by phenytoin, decrease in saquinavir levels	●	Avoid concurrent use; consider alternative agents such as gabapentin. Monitor phenytoin levels, adjust dosage
	Ketoconazole	Inhibition of CYP450 3A4 by ketoconazole, leading to increased effects of saquinavir	●	Dose adjustments not established but required
	Grape fruit	Inhibition of gastrointestinal CYP450 3A4 by grapefruit juice. Saquinavir AUC: increased 50% Oral bioavailability: increased 100%, with increased saquinavir effects	●	Separate use of grapefruit juice from saquinavir administration by at least 2 hours
	Clarithromycin	Inhibition of CYP450 3A4 by clarithromycin. Clarithromycin AUC: increased 45%	●	Dose adjustments not established but required

	Dexamethasone	Possible induction of CYP450 3A4 by dexamethasone. May decrease saquinavir levels	●	No dose adjustment necessary
	Erythromycin	Inhibition of CYP450 3A4 by erythromycin. Increased saquinavir effects	●	Dose adjustment not established
Zidovudine	Stavudine	The thymidine analogues both compete for the same phosphorylation sites in the growing chain of HIV-DNA virus	●	Never use the two drugs concurrently
	Fluconazole	Zidovudine AUC: increased 74%; Half-life: increased 128%. Increased zidovudine effects.	●	No dose adjustment necessary
	Rifampin	Rifampicin is contra-indicated with all PI and NNRTI except ritonavir and saquinavir	●	Avoid concurrent use; use saquinavir 400 mg BID with ritonavir 400 mg BID

	Valproic acid	Inhibition of glucuronidation. Zidovudine AUC: increased 79%. Increased zidovudine effects.	●	No dose adjustment necessary
	Phenytoin	Zidovudine's clearance decreased by 30%	●	No dose adjustment necessary
	Clarithromycin	Zidovudine Cmax: increased 50%; AUC: no significant change	●	No dose adjustment necessary
Lamivudine	Cotrimoxazole	Lamivudine AUC: increased 44%. Increased lamivudine effects	●	No dose adjustment necessary
Zidovudine/ Lamivudine	Stavudine	The thymidine analogues both compete for the same phosphorylation sites in the growing chain of HIV DNA	●	Avoid concurrent use
	Valproic acid	Zidovudine AUC: increased 19.5%; Cmax: increased 62%. Increased zidovudine effects	●	Monitor and adjust dose as required

	Ganciclovir	Zidovudine AUC: increased 19.5%; Cmax: increased 62%. Increased zidovudine effects	●	Monitor and adjust dosage accordingly
	Cotrimoxazole	Lamivudine AUC: increased 44%. Increased lamivudine effects	●	No dose adjustment necessary
Stavudine	Zidovudine	Intracellular activation of stavudine is inhibited	●	Avoid concurrent use
	Didanosine	Concurrent use increases risk of neuropathy	●	Avoid concurrent use
	Ethambutol	Concurrent use increases risk of neuropathy	●	Avoid concurrent use
	Ethionamide	Concurrent use increases risk of neuropathy.	●	Avoid concurrent use
	Isoniazid	Concurrent use increases risk of neuropathy	●	Avoid concurrent use
	Dapsone	Concurrent use increases risk of neuropathy	●	Avoid concurrent use
	Zalcitabine	Increases risk of neuropathy	●	Avoid concurrent use

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.	•	Caution required
	Clarithromycin	Concurrent use causes the clarithromycin AUC and Cmax to be decreased by 39% and 26% respectively	•	Avoid concurrent use. Consider using azithromycin instead
	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 1 to 2 weeks or longer	•	When using the two drugs concurrently, monitor the patients for signs & symptoms of methadone withdrawal

	Rifampin	Concurrent use of efavirenz with rifampin has been shown to reduce the AUC and Cmax of efavirenz by 26% and 20% respectively	•	Increase efavirenz dosage to 800mg daily. Substitute rifampin with rifabutin.
	Phenytoin	Phenytoin induces the CYP450-system. Reduced drug levels of efavirenz may occur	•	Avoid concurrent use
	Phenobarbital	induces the CYP450 system. Reduced drug levels of efavirenz	•	Avoid concurrent use
	Atazanavir	Both the atazanavir and the efavirenz affect the CYP3A4 system. The AUC of Atazanavir is reduced by about 74%	•	When the two drugs are used concurrently reduce atazanavir dosage to 300mg once daily and add ritonavir 100mg once daily
	Indinavir	Both the indinavir and the efavirenz affect the CYP3A4 system	•	Increase indinavir dosage to 1000mg every eight hours

	Amprenavir	The amprenavir and the efavirenz have an antagonistic effect on the CYP3A4 system.	●	Use standard dose for efavirenz, but increase amprenavir dosage to 1,200mg three times daily
	Lopinavir	Lopinavir and efavirenz have an antagonistic effect on the CYP3A4 system. Lopinavir levels may be reduced	●	Use standard dose for efavirenz, but increase lopinavir/ritonavir dosage to 533mg/133mg twice daily
	Ritonavir	Ritonavir and efavirenz have an antagonistic effect on the CYP3A4 system. Ritonavir levels may be reduced	●	Use standard dose for efavirenz, but increase lopinavir/ritonavir dosage to 533mg/133mg twice daily
	Antacids	No significant effects	●	No dosage adjustments necessary
	Carbamazepine	Induction of CYP450 and CYP3A4 by both drugs may lead to decreased effects of efavirenz	●	Avoid concurrent use. Consider alternative agents. Monitor carbamazepine levels and adjust dosage accordingly

	Ergotamine	Inhibition of CYP450 3A4 by efavirenz. Increased ergotamine effects (ergotism)	●	Avoid concurrent use
	Fluconazole	Inhibition of CYP450 3A4 by fluconazole. Efavirenz AUC: increased by 16%	●	No dose adjustment necessary
	Itraconazole	Induction of CYP450 3A4 by efavirenz. Decreased itraconazole effects	●	Avoid concurrent use
	Lorazepam	Lorazepam AUC: no significant change; Cmax: increased by 16%	●	No dose adjustment necessary
	Phenobarbital	Induction of CYP450 3A4 by Phenobarbital. Decreased efavirenz effects	●	Avoid combination if possible; consider alternative agents; monitor phenobarbital levels and adjust dosage accordingly
	Sir John's wort	Decreased efavirenz effects	●	Avoid concurrent use

	Warfarin	Possible inhibition or induction of CYP450 by efavirenz. Increased or decreased warfarin effects (altered INR, increased risk of bleeding or clotting)	●	Monitor INR and adjust warfarin dosage accordingly
	Phenytoin	Induction of CYP450 3A4 by both drug. Decreased efavirenz and phenytoin effects.	●	Avoid concurrent use; consider alternative agents; monitor phenytoin levels
	Ketoconazole	Induction of CYP450 3A4 by efavirenz. Decreased ketoconazole effects	●	Avoid concurrent use
	Azithromycin	Azithromycin AUC: no significant change; Cmax: increased 22%.	●	No dose adjustment necessary

	Clarithromycin	Inhibition of CYP450 3A4 by efavirenz. Clarithromycin AUC: decreased 39%; Cmax: decreased 26%; 14-hydroxy clarithromycin AUC: increased 34%; Cmax: increased 49%	•	Dose adjustment not established but required. Consider using azithromycin instead
	Ethinyl Oestradiol	Ethinyl estradiol AUC: increased 37%; Cmax: no significant change.	•	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 isoenzymes. Effects are seen after about one to two weeks or longer.	•	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 addition of nevirapine
	Oral contraceptives	Contraceptive failure may occur due to induction of CYP3A4 by NVP	•	Use an alternative birth control methods

	Rifampin	Rifampin and rifabutin are potent CYP3A4 inducers which reduce NVP trough levels by 37% and 16% respectively	•	In patients taking anti-mycobacterial therapy substitute rifampin with rifabutin but caution is required
	Phenytoin	Phenytoin induces the CYP450 sytem .Reduced drug levels of NVP may occur	•	Avoid concurrent use
	Carbamazepine	Carbamazepine induces the CYP450 sytem .Reduced drug levels of NVP may occur.	•	Avoid concurrent use
	Phenobarbital	induces the CYP450 sytem .Reduced drug levels of NVP	•	Avoid concurrent use
	Indinavir	The indinavir and nevirapine have an antagonistic effect on the CYP3A4 system.	•	Increase indinavir dosage to 1000mg every eight hours

	Amprenavir	The amprenavir and NVP have an antagonistic effect on affect the CYP3A4 system, levels of amprenavir may be reduced	•	Use standard dose for NVP but increase amprenavir dosage to 1,200mg three times daily
	Lopinavir	The lopinavir and NVP have an antagonistic effect the CYP3A4 system. Lopinavir levels may be reduced	•	Use standard dose for NVP, but increase lopinavir/ritonavir dosage to 533mg/133mg twice daily
	Ritonavir	The ritonavir and NVP have an antagonistic effect on the CYP3A4 system. The ritonavir levels may be reduced	•	Use standard dose for NVP, but increase lopinavir /ritonavir dosage to 533mg/133mg twice daily
	Sir John's wort	Induction of CYP450 3A4 by St. John's Wort	•	Avoid concurrent use r
	Warfarin	Alteration of warfarin effects (altered INR, or increased risk of clotting)	•	Monitor INR and adjust warfarin dosage accordingly

	Ketoconazole	Induction of CYP450 3A4 by nevirapine. Ketoconazole AUC: decreased by 63% and Cmax by 40%; Decreased ketoconazole effects	●	Avoid concurrent use
	Cimetidine	Inhibition of CYP450 3A4 by cimetidine.	●	No dose adjustment necessary
	Clarithromycin	Clarithromycin AUC decreased by 29%; Cmax by 20%; Cmin by 46%; 14-hydroxy clarithromycin AUC increased by 27%	●	No dose adjustment necessary. May consider azithromycin instead
	Ethinyl estradiol	Induction of CYP450 3A4 by nevirapine. Ethinyl estradiol: AUC decreased by 23%; half-life by 44%; Norethindrone: AUC decreased by 18%; half-life by 15%. Possible contraceptive failure	●	Avoid concurrent use; additional contraceptive measures are needed

Didanosine (ddl)	Tetracycline, Doxycycline	Magnesium and calcium ions contained in the tablet's buffer chelate these antibiotics	•	To minimize interaction Didanosine should be taken at least two hours apart
	Atazanavir	The buffer in didanosine neutralizes the acid environment needed for atazanavir absorption	•	Didanosine buffered tablets should be taken two hours apart
	Tenofovir	The ddl AUC increases by 60%	•	Dosage adjustment according to weight: if >60kg, 250mg ddl once daily; if <60kg, 200mg daily
	Allopurinol	Inhibition of presystemic metabolism by allopurinol. AUC of ddl increased between 113%-122%. Cmax increased 69-116%. Increased ddl effects (pancreatitis, neuropathy)	•	Dosage adjustment required but not established. Consider reducing ddl dose by 50%

	Ciprofloxacin	Chelation and adsorption of ciprofloxacin by divalent and trivalent ions contained in the ddl buffer. AUC decreased 16% Cmax decreased 28%.	•	To minimize interaction Didanosine should be taken at least two hours apart
	Foods	Didanosine AUC decreased by 20% with various foods; Decreased didanosine effects reported (reduction in bioavailability by 20-25% when given with any food)	•	Advise administration of didanosine at least 2 hours apart
	Itraconazole	Decreased itraconazole absorption due to decreased gastric acidity resulting from the buffer contained within didanosine tablets and suspension. Decreased itraconazole effects	•	Administer itraconazole capsules at least 2 hours after didanosine tablets/suspension. Itraconazole solution as suggested alternative

	Ranitidine	Inhibition of gastric acid slightly enhancing didanosine bioavailability by reducing acid degradation. Ranitidine AUC: decreased by 16%	●	No dose adjustment necessary
	Metroclopramide	No significant change to didanosine levels	●	No dose adjustment necessary
	Loperamide	Didanosine Cmax: decreased by 23%	●	No dose adjustment necessary
	Ketoconazole	Decreased ketoconazole absorption. Possibly decreased didanosine effects	●	Consider didanosine enteric coated or administer ketoconazole at least 2 hours apart
	Ganciclovir	Didanosine AUC: increased by 111%, but Ganciclovir AUC decreased by 21%	●	Administer at least 2 hours apart

Legend:

- Green => no clinically significant interaction, no action required
- Blue => potentially clinically significant interaction, require close monitoring, dose or and timing adjustment as indicated
- Red => clinically significant interaction, these drugs should not be administered at together , not at the same time

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:

- www.hivinsite.ucsf.edu
- www.hiv-druginteractions.org
- www.tthivclinic.com
- www.aids-etc.org
- www.rx.com
- www.unaids.org
- www.medadvocates.org/marg/children/HIVTreatmentGuidelines/
-

2. Books

- South African Medicine Formulary. 6th Edition.
- National Antiretroviral guidelines. 2004

3. Package inserts of registered ARV drugs