Kingdom of Cambodia
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Ministry of Health

National Guidelines for the use of Antiretroviral Therapy in Adults and Adolescents

Revised in
March 2007

National Center for HIV/AIDS, Dermatology and STD

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Preface

The HIV prevalence in Cambodia has declined since 1998. This gradual reduction of the prevalence was recognized by both the national and international community, for instance, the sero prevalence among the adult population aged 15 to 49 year-old declined from 3% in 1998, to 1.9% in 2003 based on the results of NCHADS HIV Sentinel Surveillance. Although the prevalence has decreased, the estimated number of people living with HIV was 123,100 people and 20,000 developed AIDS, who urgently need care and treatment.

The Ministry of Health, through the National Center for HIV/AIDS, Dermatology and STI (NCHADS), set the targets and strategies to provide care and treatment services for PLHAs, especially Antiretroviral Treatment. OI/ART clinics were fully integrated into the health care system, and the clinics have been strengthened and scaled-up to 44 sites by 2006, including clinics managed by NGOs. In 2006, 20,131 PLHAs, including 1,787 children, have received antiretroviral treatment.

NCHADS has a culture to work with all partners, national and international experts who provide ART to actively participate in the review of these essential national guidelines and complete them as planned. In the same year, NCHADS, in collaboration with national and international experts, has reviewed the national guidelines for antiretroviral therapy in adults and adolescents in order to adapt according to the current situation. This will benefit all health care workers for public, NGOs and private hospitals in providing high-quality care and minimize the resistance to antiretroviral drugs.

The national guidelines for the use of antiretroviral therapy was reviewed and approved in 2006 by the Ministry of Health. We strongly hope that the health care workers in public, NGOs, and private health care systems will take responsibility to implement this national policy to achieve good results and improve the good health of PLHAs.

Phnom Penh, ...March 2007

Acknowledgement

The National Center for HIV/AIDS, Dermatology and STI wishes to thank all national and international experts for their efforts to revise the national guideline for the use of antiretroviral therapy in adults and adolescents. NCHADS would like to take this opportunity to express our deep thanks to the technical working groups, in which members from national and international institutions, NGOs as well as civil societies, who active participated with strong commitment to develop this document. These members were from Calmette hospital, Khmer-soviet hospital, Prea Ket Mealea Hospital, Kosamak hospital, referral hospitals/operational districts, CTAP, Center of Hope, MSF France and Belgium, WHO, UNAIDS, FHI, ESTHER, CDC-GAP, CRC France, CHAI, UNSW/NCHADS, Maryknoll, CPN+, and CARE-Cambodia. NCHADS thanks all members for their cooperation and valuable support.

NCHADS would also like to thank the AIDS CARE Unit staff and Dr. Julian Elliot for their efforts in coordination and cooperation with all partners to achieve this great input.

Phnom Penh,.....March 2007

Dr. Mean Chhi Vun
Director of NCHADS

Abbreviations

3TC	Lamivudine
ABC	Abacavir
AIDS	Acquired Immunodeficiency Syndrome
ALT	Alanine Transaminase
AST	Aspartate Transaminase
ARV	Antiretroviral drug(s)
AZT	Zidovudine
CBC	Complete Blood Count
CD4	T-CD4+ Lymphocyte
CMV	Cytomegalovirus
CNS	Central Nervous System
CK	Creatine Kinase
CrCl	Creatinine Clearance
d4T	Stavudine
ddI	Didanosine
DOT	Directly Observed Therapy
EC	Enteric Coated
EFV	Efavirenz
EPTB	Extra-pulmonary Tuberculosis
ESRF	End Stage Renal Failure (Dialysis dependent)
FDC	Fixed Dose Combination
HAART	Highly Active Antiretroviral Therapy
HGC	Hard Gelatin Capsules
HIV	Human Immunodeficiency Virus
IDV	Indinavir
IPT	Isoniazid Preventive Therapy
LDH	Lactate Dehydrogenase
LDL	Low-Density Lipoprotein
LPV	Lopinavir
LPV/RTV	Lopinavir/Ritonavir
MTCT	Mother to Child Transmission
NFV	Nelfinavir
NNRTI	Non-Nucleoside Reverse Transcriptase Inhibitor
NRTI	Nucleoside Reverse Transcriptase Inhibitor
NtRTI	Nucleotide Reverse Transcriptase Inhibitor
NVP	Nevirapine
OHL	Oral Hairy Leukoplakia

OI	HIV related Opportunistic Infection
PCP	*Pneumocystis carinii* pneumonia
PLHA	Person/people living with HIV/AIDS
PI	Protease Inhibitor
PID	Pelvic Inflammatory Disease
PMTCT	Prevention of Mother to Child Transmission
PPD	Purified Protein Derivative (skin test for tuberculosis)
PPE	Papular Pruritic Eruption
PTB	Pulmonary Tuberculosis
R	Ritonavir (when given in association with other PIs for boosting effect)
RTV	Ritonavir
SGC	Soft Gelatin Capsules
STI	Sexually Transmitted Infection
SQV	Saquinavir
TB	Tuberculosis
TDF	Tenofovir
TST	Tuberculin Skin Test
VCT	HIV voluntary counseling and testing
VDRL	Venereal Diseases Reference Laboratory (refers to a test for syphilis)

1. Introduction

In April 2006, Cambodia's achievements in meeting national targets set under the World Health Organization's (WHO) 3 by 5 Initiative for increasing access to care and treatment to 12,355 people living with HIV/AIDS by the end of 2005, were recognized in a ceremony attended by the WHO's Regional Director. Within four years of implementing the Continuum of Care framework and publishing the 1st edition of the National ARV Treatment Guidelines, the number of patients receiving ARV treatment grew to over 20,000 patients nationwide. The urgency of preventing the illness, disability and death of people living with HIV/AIDS in Cambodia remains as strong as ever. It also strengthens prevention efforts by encouraging testing, reducing stigma and discrimination and potentially reducing transmission. The drugs are not a cure and there are problems associated with treatment, but life expectancy, quality of life, perception of HIV and health care utilization have all been transformed.

To ensure the quality of care of ART, the Ministry of Health agreed to officially implement the National Guidelines for the Use of Antiretroviral Therapy for Adults and Adolescents, which were approved in 2001 and revised later in 2003. These national guidelines do not seek to address the complex operational requirements of comprehensive HIV care in general, nor of ARV provision in particular.

2. What is antiretroviral therapy?

Antiretroviral (ARV) therapy refers to medicines that are active against the HIV virus. They act by inhibiting the enzymes that are needed by HIV in order for it to replicate and infect cells. The ARVs available in Cambodia target the following enzymes:

- Reverse transcriptase
- Protease

ARV drugs in use in Cambodia are divided into 4 main classes. Three of the classes inhibit reverse transcriptase and one class inhibits protease:

- Nucleoside Reverse Transcriptase Inhibitors (NRTI)
- Nucleotide Reverse Transcriptase Inhibitors (NtRTI)
- Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTI)
- Protease Inhibitors (PI)

Three more classes of ARV have shown activity against HIV, including Entry, Integrase, and Maturation inhibitors. However, at present they are not widely available as many are still under development.

The ARV drugs included in these guidelines are those that have sufficient potency and ease of use to be acceptable for use in Cambodia at the present time.

- NRTI: Zidovudine (AZT or ZDV)
  Stavudine (d4T)
  Lamivudine (3TC)
  Didanosine (ddI)
  Abacavir (ABC)
- NtRTI Tenofovir (TDF)
- NNRTI Nevirapine (NVP)
  Efavirenz (EFV)
- PI Nelfinavir (NFV)

Indinavir and low dose Ritonavir (IDV/r)
Lopinavir and low dose Ritonavir (LPV/r)
Saquinavir and low dose Ritonavir (SQV/r)

PIs are preferably administered together with Ritonavir (RTV). Although RTV is a potent ARV drug itself, its side effects limit its use in its own right. It can however be used at low dose in order to reduce the metabolism of the other PI, enabling less frequent dosing. Ritonavir must be given as a separate tablet except for LPV/r where a combination capsule is available.

Most ARV drugs recommended for use in Cambodia are available as fixed dose combinations (products with two or more ARV drugs in a single tablet or capsule) and qualified by WHO, including:

- Zidovudine + Lamivudine (AZT + 3TC)
- Stavudine + Lamivudine (d4T + 3TC)
- Zidovudine + Lamivudine + Nevirapine (AZT + 3TC + NVP)
- Stavudine + Lamivudine + Nevirapine (d4T + 3TC + NVP)

3. Principles of antiretroviral therapy

The aims of ARV therapy are:

- Maximal and durable suppression of HIV replication
- Restoration of immune function
- Improved quality of life
- Reduction of HIV related morbidity and mortality
- Prevention of viral resistance and treatment failure
- Prevention of MTCT

The only ARV treatment regimens able to reliably achieve and maintain the aims listed above are combinations of at least three potent ARV drugs. These combinations are also known as Highly Active Antiretroviral Therapy (HAART).

Potent ARV combinations can rapidly suppress the replication of HIV. This leads to a rapid fall in the amount of HIV in the blood (known as the HIV 'viral load') to below the limit of detection by currently available assays. This reduces the impact of HIV on the immune system and leads to a gradual restoration of immune function, both in terms of *quantity* (as measured by CD4 count) and *quality*.

The process of immune restoration is gradual, occurring over many months or even years, and is not perfect. Some risk of opportunistic infection or other HIV related illness persists at least for a time, necessitating the use of OI prophylaxis and ongoing monitoring for new HIV related illness in many people taking ARVs.

ARV therapy is not a cure. It suppresses HIV replication, but does not eradicate the virus. If ARV therapy is ceased HIV replication quickly returns to pre-treatment levels and promptly begins to damage the immune system once again.

HIV develops spontaneous genetic mutations at a very high rate. Effective combination ARV therapy reduces the rate of development of these mutations by continuously suppressing HIV viral load to very low levels. If sub-optimal ARV therapy is used (for example, inappropriate combinations or intermittent dosing) the combination of ongoing viral replication and the presence of ARV drug will lead to the growth of viral populations that carry a genetic mutation which protects against these drugs. Eventually this population will become dominant and the particular ARV

combination being used will become ineffective. This resistant virus population may also be transmitted to others.

4. Starting antiretroviral therapy

4.1 Confirm HIV infection

Consider HIV under the following circumstances:

- Risk behavior (sexual behavior, drug use)
- Pregnancy
- Sexually transmitted infection
- Tuberculosis (TB)
- Clinical suggestion of HIV infection (See Table 1 below)

All health care workers should provide information on the importance of HIV testing and should refer patients to VCCT with their consent.

Table 1: Basic HIV facts

HIV is a virus that weakens the body's ability to protect itself against other illnesses
AIDS is the illness that occurs when the body's defenses have been weakened by HIV
HIV can be spread by sexual intercourse via blood, semen or vaginal fluids
HIV can also be transmitted by blood transfusion, reusing needles or from mother to child during pregnancy, labor or breast feeding
HIV cannot be transmitted by normal social contact, kissing, sharing food or by insects
Someone can be infected with HIV and be well for many years
Treatment can control HIV infection, but cannot cure it

4.2 First Doctor Visit

- Assess past medical history including TB, PMTCT and ARV treatment
- Investigate and treat current illnesses as clinically indicated *(please see table 2 on page 11 for physical evaluation criteria*)
- Assess current WHO clinical stage
- Perform routine investigations, e.g. CD4 count
- Refer for basic counseling

Table 2: Criteria for starting ARV

WHO Clinical Stage	Action
Stage I, II or III	ART if CD4 cell count ≤ 250 cells/mm^3 and patient fulfills psycho-social criteria
Stage IV	Irrespective of CD4 count, ART for all* who fulfill psychosocial criteria
*Extra-pulmonary TB and CD4 cell count > 250 cells/mm^3: defer ART	

4.3 Second Doctor Visit

- Continue investigation and treatment of current illnesses
- Check results of routine investigations and assess eligibility for ART
- Perform routine pre-ART tests if indicated, e.g. CBC, SGPT/ALAT, CXR
- Refer for pre-ART counseling if indicated (> 1 visit to counselors; see table 1 below)

Table 3: Recommended laboratory monitoring during ARV therapy

Laboratory monitoring		
Laboratory test	**Before ART**	**During ART**
HIV antibody	Essential for all	Not required
CD4 count	Essential for all	Essential every 6 months
Hemoglobin	Essential if using AZT	Recommended at M1, M2, M3, every 3-6 months if using AZT
SGPT / ALAT	Recommended if using NVP or EFV	Recommended at M1, M2, M3, every 3-6 months if using NVP or EFV
Pregnancy test	Essential if using EFV	Essential if using EFV and pregnancy suspected
CBC	Recommended for all	Optional every 3-6 months
Chest X-ray	Recommended for all	If clinically indicated (TB)
HIV viral load	Not required	Optional if treatment failure is suspected
Creatinine	Optional for all Essential if using IDV or TDF	Optional every 6-12 months
Phosphate	Optional if using TDF	Optional every 3-6 months if using TDF
Amylase	If clinically indicated	If clinically indicated
Lipids	Optional if using d4T or a PI	Optional every 12 months if using d4T or a PI
Hepatitis B / C serology	Optional for all	Not required

4.4 Third Doctor Visit

- Continue investigation and treatment of current illnesses
- Check results of routine pre-ART investigations
- Decide if ART can be started.
- Check understanding of HIV and ART. The success of ART is dependent on the understanding and commitment of the individual taking ARV. Defer ART and refer for more counseling if understanding of adherence is not good.
- If doctor and patient decide to start ART, choose ART regimen (Table 4)

Table 4: Standard ARV first line regimens

Situation	Regimen
Standard first line ART regimen	**d4T + 3TC + NVP**
Alternative first line ART regimens for special cases	
Pregnancy	AZT + 3TC + NVP
Neuropathy	AZT + 3TC + NVP
Neuropathy and anaemia	Seek expert advice
TB treatment using rifampicin with no neuropathy	d4T + 3TC + EFV
TB treatment using rifampicin with neuropathy	AZT + 3TC + EFV
TB treatment using rifampicin with pregnancy	Seek expert advice
SGPT/ALAT > 5 times upper limit of normal	d4T + 3TC + EFV
SGPT/ALAT > 5 times upper limit of normal with pregnancy	Seek expert advice
Previous ART experience	Seek expert advice
Standard second line ART regimen	**TDF+3TC+LPV/RTV** or DDI+3TC+LPV/RTV

The risk of NVP side effects (especially rashes) can be reduced by starting with a lower dose of NVP. For the first two weeks give d4T+3TC+NVP as one of the daily doses and d4T+3TC alone as the other daily dose, then increase to the full dose of one d4T+3TC+NVP tablet twice a day.

5. People co-infected with TB

Start TB therapy immediately after diagnosis of TB and in association with cotrimoxazole prophylaxis for PCP. The optimal time to start ARVs is not known. If ARV therapy is started early there is a high rate of drug side effects and immune restoration inflammatory syndrome (IRIS), which is the exacerbation of previously sub-clinical TB symptoms when the patient recovers immune function. If ARV therapy is started late there is a high risk of other HIV-related illnesses and opportunistic infections (OIs), particularly for people with low CD4 counts. See Table 5 below.

The choice of ARV is complicated by the use of rifampacin throughout TB treatment. In most circumstances d4t + 3TC + EFV can be used (Table 4). Women should use effective contraception and should not use EFV during the first trimester of pregnancy. Standard doses of NVP can be used instead.

If neurotherapy is present AZT should be used instead of d4T. In this situation, NVP is an option of last resort as correct dosing has not been established, and because NVP has overlapping hepatotoxicity with TB therapy.

People who develop TB whilst on ART should have their ARV combination adjusted by shifting NVP to EFV. After completion of TB treatment, NVP can be substituted for EFV unless CD4 count is >250 cells/mm^3 in men.

Table 5: Initiating ARV treatment in patients with TB

CD4 cell count	Action
< 200	• Start TB treatment • Start ART after 2-8 weeks of TB treatment, as soon as TB treatment is tolerated. Use EFV*-containing regimen unless pregnant
200-250	• Start TB treatment. • Start ART after the initiation phase (8 weeks) • Use EFV*-containing regimen unless pregnant
> 250	• Start TB treatment • Defer ART

6. Pregnant women and women of childbearing potential

- Recommended ART during pregnancy is AZT + 3TC + NVP.

- EFV should not be used during first trimester due to the risk of teratogenicity. The risk of lactic acidosis/hepatic steatosis is increased during pregnancy. EFV can be continued during 2nd and 3rd trimesters. Do not use d4T+ddI unless there are no other treatment options, as this combination increases the risk further. The safety of TDF during pregnancy is not year clearly defined. TDF should only be used during pregnancy if there are clear advantages for the mother's health when compared to the use of alternative agents, e.g. second-line therapy due to drug resistance. There

are more data on the safety of SQV/r during pregnancy than LPV/r. If LPV/r is used, standard doses should be used.

- It is acceptable to use NNRTIs in a treatment combination if a pregnant woman has previously received only single dose NVP without other ARV for PMTCT.

- Women who are not on ART at the start of pregnancy should start ART whenever it is indicated. If ART is started during pregnancy, ART should continue after delivery.

- Women on ART who become pregnant should continue ARV therapy. The ARV regimen should be optimized to ensure the lowest possible maternal HIV viral load at the time of delivery, as this point is the most important predictor of MTCT. If pregnancy is recognized during the first trimester, EFV should be changed to another agent.

- Continue ART during labor. ARV prophylaxis should be given to the baby (refer to National Guidelines for PMTCT).

- Pay extra attention to adherence during and after pregnancy, as adherence to ART can be particularly difficult during this time. Adherence is important not only for the health of the mother, but also to reduce transmission to the child.

- Counsel mothers on ART about their infant feeding options, as per the National Guidelines on PMTCT. Women taking ARVs who decide to breastfeed should continue taking ARVs.

- NVP and most PIs lower blood levels of oral contraceptive pills (OCP), so additional or alternative methods of contraception should be used (ie condoms). The exact interactions between EFV and hormonal contraception, or between ARV and injectable hormonal contraception, are not clearly known. Additional or alternative methods of contraception (ie condoms) should be used in these situations as well.

Table 6: Initiating ARV prophylaxis and treatment in pregnant women

ART eligibility	Mother	Infant
Eligible (WHO stage 4 or CD4 < 250)	• Start AZT+3TC+NVP[1] (d4T+3TC+NVP if anemia)	• Single dose NVP at birth[2] • AZT for one week[3]
Not eligible (or HAART not available)	• AZT[1] from 28 weeks of pregnancy and during labor[4]. • Single dose NVP at onset of labor. • AZT+3TC for 7 days after delivery	• Single dose NVP at birth[2] • AZT for one week[3]
Mother presents after delivery	• Assess for ART using routine procedures	• Single dose NVP[2] • AZT for four weeks
[1]Check hemoglobin/hematocrit. If hemoglobin <90 g/l or hematocrit <33% treat anemia		

before using AZT. If eligible for HAART use d4T-containing regimen instead of AZT-containing.
[2]A single dose of NVP 2mg/kg within 72 hours of birth
[3]If mother received < 4 weeks of ARV during pregnancy; AZT should be given to the infant for 4 weeks.
[4]AZT 300mg at onset of labor and every 3 hours until delivery

7. People who have taken ARV therapy previously

Initiating ARV therapy in people who are 'ARV experienced' is complicated and should be done in consultation with an expert physician experienced in ARV therapy.

Taking an appropriate combination of three potent ARV drugs for a period of time and ceasing all drugs at the same time does not carry a high risk of resistance. Evaluate whether ARV therapy is indicated and if so restart an appropriate and potent triple-ARV combination. Use the original combination if this was appropriate, well tolerated and taken correctly.

People who have taken NRTI monotherapy or bi-therapy for less than 2-3 months should generally be changed to 3 potent ARV drugs.

People who have taken NRTI monotherapy or bi-therapy for more than 2-3 months have a significant risk of having NRTI resistant HIV strains. Management of this group is complicated. One approach is to start standard first line therapy. If treatment failure occurs, the most effective regimen possible should be given including NRTI, NNRTI and/or PI classes.

The management of people who have taken other inappropriate ARV combinations should be individualized based on previous treatment history. If this is not known, first line ARV therapy can be used (d4T+3TC+NVP), with close monitoring for treatment failure.

8. People co-infected with hepatitis B and/or hepatitis C

Hepatotoxicity of ARVs is increased approximately 3-fold in people co-infected with hepatitis B or C. However, symptomatic hepatitis remains uncommon (1-2%).

NVP and the combination of d4T + ddI should be avoided in PLHA with abnormal LFTs (raised ALT, AST or bilirubin).

3TC and TDF are active against hepatitis B, but the optimal use of these agents in hepatitis co-infected people has not been established and is difficult to determine in the absence of specialized tests. If it is thought that HIV resistance has diminished the possible anti-HIV effect of these agents, they can be continued for their anti-hepatitis-B effect together with 3 effective anti-HIV ARV agents.

There is a risk of "hepatitis flare" in patients with hepatitis B if 3TC or TDF are ceased.

9. People with other opportunistic infections (OIs)

Simultaneous use of ART with treatment of OIs other than TB is not limited by difficult drug interactions and should be feasible in most situations.

In most situations it is preferable to delay the start of ARV therapy until there are indications that the opportunistic infection has begun to be controlled. Do not start cotrimoxazole and NVP at the same time, because the cause of any rash that develops

would be difficult to determine. However, note that all ARV should be started at the same time.

For OIs where effective treatment is unavailable, give ART early as immune recovery will likely be beneficial.

OI prophylaxis should be given according to the National Guidelines on Prophylaxis of Opportunistic Infections.

10. Continuing antiretroviral therapy

10.1 Support ARV adherence

'Adherence' is taking medication continuously--not missing or delaying doses of medicines. It is the key factor in the success of ARV therapy. Poor adherence leads to treatment failure, drug resistant HIV, reduced treatment options and increased cost of ARV regimens. Nevertheless, adherence to daily, lifelong medication is hard work. No one can achieve perfect adherence all the time.

The assessment of an individual's adherence to ART by health care workers is often inaccurate. Health care workers should spend more time supporting adherence than trying to assess it. The best way to support adherence is to focus on the needs of the person taking ARVs. Practical ways to support adherence include working with the person to problem-solve difficulties with taking their ARVs, referring them to a support group or MMM, encouraging them to find an 'adherence supporter' or 'buddy,' and linking them with an HBC team.

Encourage people taking ARVs to become actively involved in their own care. Assist them to understand HIV and its treatment, to identify their own barriers to adherence and to find ways to overcome these barriers. Directly observed therapy (DOT) is not recommended as it is unlikely to be sustainable in the long term. Explore the risks and benefits of disclosure of HIV status. Whilst support from friends and family can significantly improve adherence, stigma and discrimination can undermine adherence.

Identify and address mental health issues, particularly depression and the use and abuse of harmful substances.

Minimize the 'pill burden', the number of tablets required each day.

ARV side effects reduce adherence. Encourage people taking ARV to report new symptoms whenever they develop. Check for side effects at each visit and deal with them promptly. Particularly important are nausea, vomiting and diarrhea, and, in the longer term, lipodystrophy.

Voluntary interruption of ARV therapy is not recommended, as it is associated with risks of seroconversion illness and OIs, particularly in those with low CD4 counts.

Adherence is a continuous process. Talk about it at every visit.

10.2 Monitor ARV therapy

- Anyone starting ART should see their doctor:
  - 4 weeks after starting ARV (2 weeks if possible)

- Monthly until they understand ART regimen and adherence, and until there are no new medical problems
- Then at least every 3 months, with monthly visits to pick up medication and discuss adherence and any new symptoms with a member of the treatment team.

- Emphasize to people taking ARV the importance of reporting new symptoms as soon as possible. Ask about and examine for new signs and symptoms at each visit. Determine whether they are due to:
  - New illness, including a new OI (See Table 2, page 11)
  - Drug side effects
  - Immune reconstitution (See page 17)
- Perform regular laboratory monitoring (See Table 5, page 16). Additional investigations should be performed as clinically indicated.

10.3 Diagnose and manage opportunistic infections

- Despite successful ARV therapy, OIs can still occur. See Table 2 (page 11) for a brief list of signs and symptoms that may be due to OIs and 'Guidelines For The Clinical Management of HIV Infection In Adults' for more detailed guidance on the diagnosis and management of OIs. The development of an OI may indicate treatment failure (see Section 14)

10.4 Diagnose and manage ARV side effects

- OI/ART clinicians and counselors have the main responsibility to explain to people taking ARV the most common side effects of their ARV combination. Drug side effects usually occur in the first few weeks and are usually mild and resolve after a month or so. Side effects can, however, occur at any time and can be serious. See Table 6, section 14, Annex 2 and Table 10 for advice on the management of side effects.

10.5 Diagnose and manage immune restoration disease (IRD) / immune reconstitution inflammatory syndrome (IRIS)

- The symptoms and signs of many infections are partly due to the reaction that they provoke from the immune system. When ARV therapy is given it strengthens the immune reaction to infections, leading to an appearance or increase in various clinical manifestations. This can result in:
  - Previously asymptomatic infections becoming symptomatic
  - Apparent worsening of symptomatic infections even if they are being successfully treated.

- These manifestations are not a result of an infection alone or the immune system alone, but are due to an interaction between the two. They usually occur a few weeks after commencing ARV, but can occur any time in the first 3-6 months of ARV therapy, or, in rare cases, later.

- The most important immune reconstitution syndrome is caused by TB. This is similar to 'paradoxical reactions' seen in non-HIV infected people being treated for TB. Usually it involves fever and an increase in TB lesions: especially lymph node and/or pulmonary infiltrates, but also bronchial lesions, ureteric strictures, or CNS lesions.

- The most important aspect in this diagnosis is to differentiate between 1) drug toxicity or 2) TB treatment failure due to drug resistance or poor adherence. This can be difficult.

- The usual approach to management is
  - Continue ARV
  - Start/continue treatment for the symptomatic infection
  - A short course of corticosteroids are occasionally required if symptoms become severe (e.g. dyspnoea, CNS symptoms, renal obstruction). Non-steroidal anti-inflammatory agents can be used to reduce symptoms related to inflammation, e.g. lymphadenitis and fever.

Table 7: ARV side effects*

Drug and drug class	Class specific side effects	Drug specific side effects				
		Skin	**Blood**	**Gastrointestinal**	**Neuromuscular**	**Other**
Zidovudine (ZDV or AZT)	**Lipoatrophy** **Lactic acidosis** **Hepatic toxicity**		**Anaemia** **Neutropenia**	Nausea (common)	Headache (common) Myopathy Cardiomyopathy	
Stavudine (d4T)				**Pancreatitis** Hepatic toxicity	**Peripheral neuropathy** Guillain-Barre like syndrome	Lactic acidosis Lipoatrophy
Lamivudine (3TC)			Neutropenia (rare)	Pancreatitis (rare)	**Peripheral neuropathy** (rare) Headache (rare)	No common side effects
Didanosine (ddI)				**Pancreatitis** Diarrhea, Nausea, Vomiting, Abdominal pain	**Peripheral neuropathy**	
Abacavir (ABC)						**Hypersensitivity syndrome**
Tenofovir (TFV or TDF)						No common side effects
Nevirapine (NVP)	**Rash** **Hepatitis**	**Rash**		**Hepatitis**		Hypersensitivity syndrome
Efavirenz (EFV)		Rash		Hepatitis	**Frequent and diverse CNS effects#**	**Teratogenicity**
Nelfinavir (NFV)	**Lipodystrophy**	Rash		**Diarrhea** Abdominal pain		

Indinavir + Ritonavir (IDV/r)	**Insulin resistance and diabetes** **Hyperlipidemia** **Hepatitis** Bone disorders Increased bleeding in hemophiliacs	Alopecia, dry skin and lips		Hyperbilirubinaemia Esophageal reflux	Parasthesia	**Kidney stones**
Lopinavir + Ritonavir (LPV/r)				Diarrhea	Parasthesia	Hyperlipidaemia
Saquinavir + Ritonavir (SQV/r)				Nausea Diarrhea	Headache Parasthesia	

*Major side effects are in bold

#Includes dizziness, headache, insomnia, depression, impaired concentration, agitation, nightmares, sleepiness, severe depression, suicidal ideation, mania and delusions.

11. Minimize the development of resistance

The development of resistance is an inevitable consequence of treatment of any infectious disease. It is not a sufficient argument for withholding treatment. HIV resistance to ART reduces the efficacy of ARV therapy, increases the cost of the ARV regimen. Furthermore, ARV-resistant strains of HIV can be transmitted to others (through normal modes of transmission).

Support adherence. Imperfect adherence is the most important cause of drug-resistant HIV (See 10.1)

Use ARVs correctly. Inappropriate use of ARVs by untrained practitioners is a very important cause of drug-resistant HIV. ARVs should only be prescribed by trained doctors who can ensure appropriate ARV combinations, dosing, monitoring, supply and switching.

The Ministry of Health prohibits the prescription of fewer than three effective ARV drugs together. If an ARV drug needs to be ceased, then all ARV should be ceased until a complete ARV regimen can be restarted. Continue NRTIs for 10-14 days after NVP or EFV is ceased because the half-life of NVP/EFV is longer than the half-life of NRTIs.

Reduction in risk behavior by people taking ARVs is an important mechanism for reducing the spread of drug-resistant HIV. Adherence is also critical to reducing the amount of HIV in blood and body fluids, thereby reducing the risk of HIV transmission.

12. Provide holistic support

Provision of drugs alone is not sufficient support to PLHA. Successful ARV therapy depends upon a holistic approach to the needs of PLHA. This includes:

- Psychosocial support. Appropriate psychological support at difficult times can improve long term outcomes.
- Nutritional support. Many people who access ARV are not able to access adequate food intake. Good nutrition boosts the immune system and improves overall ARV treatment outcomes. Nutritional support should be addressed in all people taking ARVs.
- Social and financial support can help as PLHA become stronger. Income generation and training to allow return to economic independence can be particularly important.

Linkage with other available services is critical for treatment success, particularly home-based care (HBC) teams and PLHA support groups. See ‘Continuum of Care for people living with HIV/AIDS – Operational Framework’ for ways to link ARV therapy into a comprehensive care approach.

13. Support behavior change and disclosure

A good time to explore risk behavior is after a few months of ARV therapy. Ask about sexual behavior, condom use, planned pregnancies and contraception. Support the development of safe sexual practices over time.

Reinforce that PLHA should not donate blood and should make sure that no one uses a needle after they have used it, whether for medical treatment, tattooing or injecting drug use

Explore risks and benefits of disclosure of HIV status, including to sexual partners. Disclosure can ensure that others are not exposed to HIV infection and can provide greater support to PLHA, but this must be balanced against the risk of stigma and discrimination.

14. Changing antiretroviral therapy

14.1 ARV Changes because of side effects

- If needing to temporarily cease one drug, cease all drugs. Continue NRTIs for 10-14 days after NVP or EFV is ceased because the half-life of NVP/EFV is longer than the half-life of NRTIs.
- See Table 8 below. Also see Table 6, Annex 2 and Table 10 for more details.

Table 8: Changing ARV because of side effects (see sections 10.4-10.5)

Drug	Side effect	Suggested immediate action	Suggested future action
NRTI	Lipoatrophy	Consider changing NRTI (d4T or ddI or AZT) to ABC	Can use these drugs again, but will make lipoatrophy worse
	Lactic acidosis	Change NRTI to ABC or TDF	Try to avoid using AZT, d4T or ddI again
AZT	Anaemia (Hb<80 g/l or fall > 25%)	Change AZT to d4T	Avoid AZT
	Neutropenia (neutrophils < $1.0x10^6$/l)	Change AZT to d4T	Avoid AZT
d4T	Peripheral neuropathy (moderate or severe)	Change d4T to AZT	Avoid d4T
ddI	Pancreatitis and peripheral neuropathy	Change ddI to another NRTI (not d4T)	Avoid ddI
ABC	Hypersensitivity Syndrome	Change ABC to another drug depending on previous experience	Never use ABC again as reuse can be fatal
NVP	Rash – moderate to severe (eg bullae, "wet")	Change NVP to EFV	Never use NVP again
	Rash – complicated (mucosal involvement or fever)	Change NVP to PI or ABC	Never use NVP or EFV again
	Hepatitis	Change NVP to EFV	Never use NVP again
	Hepatitis – severe or life threatening	Change NVP to PI or ABC	Never use NVP or EFV again
EFV	CNS effects – severe	Change EFV to NVP	Avoid EFV
	Pregnancy (teratogenicity)	Change EFV to NVP	Can use EFV again when not pregnant
PI	Metabolic complications (hyperglycaemia, hyperlipidaemia) – uncontrolled	Change PI to non-PI if unable to be controlled	Avoid using PI again if possible
NFV	Diarrhea – severe or persistent	Change NFV to non-PI if possible (or PI/r)	Avoid using NFV again if possible
IDV	Kidney stones – repeated	Change IDV to another PI or other drug	Never use IDV again if possible

14.2 Treatment failure

Treatment failure is possible when the following occurs:

14.2.1 Clinical Failure:

- New or recurrent HIV-related illness (OI or malignancy) after at least 3 months on ART (WHO recommends at least 6-12 months on first line regimen). See also table 10 to confirm the evolution of diseases

14.2.2 Immunological Failure:

- Failure of CD4 cell count to increase by 25-50 cells/mm3 during the first 12 months of ART.

- Decrease in CD4 cell count to pre-therapy baseline level or below, without OI to explain transient CD4 cell decrease.
- > 50% fall from on-therapy CD4 peak level, without infection to explain transient CD4 cell decrease.

14.2.3 Virological Failure:

- Repeated detectable HIV viral load

Indications of possible treatment failure as described above may require switching ARV regimen. This is an important and complicated decision that should be made in consultation with an expert. See table 9 and 13 below.

Table 9: Management of suspected treatment failure: clinical

Scenario	Duration ART	Diagnosis	Action
Any new or recurrent HIV related illness	< 3 months	• Not treatment failure. • May be due to: o IRD/IRIS o Active OI because of low CD4.	• Treat HIV related illness as usual. • Consider anti-inflammatory drugs if severe symptoms due to TB-related IRD/IRIS. • Continue ART unchanged.
Any new or recurrent HIV related illness	3 – 6 months	• May be due to: o IRD/IRIS o Active OI because of low CD4. o Treatment failure (unlikely).	• Treat HIV related illness as usual. • Consider anti-inflammatory drugs if severe symptoms due to TB-related IRD/IRIS. • Continue ART unchanged. • Check clinical status and CD4 count after treatment of illness episode. If CD4 count increasing and patient clinically improving then probably not treatment failure.
WHO Clinical Stage II conditions	> 6 months	• May be due to: o Minor illness o IRD/IRIS (less common after 6 months) o Treatment failure (especially PPE)	• Treat HIV related illness as usual. • Check clinical status and CD4 count after treatment of illness episode. If CD4 count increasing and patient clinically improving then probably not treatment failure.
WHO Clinical Stage III/IV conditions (except TB)	> 6 months	• These events can occur during successful ART if CD4 count is still low • May be due to: o Persisting immune deficiency o Treatment failure o IRD/IRIS, but less common after 6 mo.	• Treat HIV related illness as usual. • Check clinical status, CD4 count and HIV viral load if available after treatment of illness episode.
TB (any form)	> 6 months	• TB can occur at any CD4 count / immune function.	• Treat TB as usual. • Consider anti-inflammatory drugs if severe symptoms due to TB-

		• May be due to: o High risk of TB in Cambodia. o IRD/IRIS (less common after 6 months) • Treatment failure	related IRD/IRIS. • Check clinical status, CD4 count and HIV viral load if available after initial treatment.

Table 10: Management of suspected treatment failure: immunological

Scenario	Duration of ART	Diagnosis	Action
CD4 cell count increase < 25-50 during first 12 months of ART	12 months	• May be due to: o Treatment failure o 'Normal' response, especially in older people o Laboratory error	• Check CD4 count and clinical status. • If clinical response to ART has been poor or if poor CD4 count increase is confirmed check HIV viral load if available.
Decrease in CD4 cell count to pre-therapy baseline or below	> 6 months	• May be due to: o Treatment failure o Intercurrent illness o Laboratory error	• Check CD4 count, especially if first CD4 count was performed during an intercurrent illness. • If CD4 count is confirmed then check HIV viral load if available.
Decrease in CD4 cell count to 50% of on-therapy peak or below	> 6 months	• May be due to: o Treatment failure o Intercurrent illness o Laboratory error	• Check CD4 count, especially if first CD4 count was performed during an intercurrent illness. • If CD4 count is confirmed then check HIV viral load if available.
Any decrease in CD4 count	> 6 months	• May be due to: o 'Normal' response, especially in older people o Treatment failure o Laboratory error	• Check CD4 count, especially if first CD4 count was performed during an intercurrent illness. • If CD4 count is confirmed then consider checking HIV viral load if available.

Table 11: Viral load testing eligibility

Adults
•Any new or recurrent WHO Clinical Stage III or IV condition, including any form of TB, occurring after at least 6 months of ART. •Failure of CD4 cell count to increase by 25-50 cells/mm^3 during the first 12 months of ART (see Annex 5, Figure 1). •Decrease in CD4 cell count to pre-therapy baseline or below without intercurrent illness to explain CD4 cell

decrease.

- Decrease in CD4 cell count to 50% of on-therapy peak or below without intercurrent illness to explain CD4 cell decrease.

- Any decrease in CD4 count may be considered as an indication for HIV viral load testing if laboratory capacity allows

Table 12: Management of suspected treatment failure: virological

Scenario	Duration of ART	Diagnosis	Action
Detectable HIV viral load	≤ 4 months	• Not treatment failure • Suppression of HIV viral load to below limit of detection may take up to 4 months after starting ART.	• Continue ART unchanged.
Detectable HIV viral load	> 4 months	• May be o Virological failure o If < 500 c/ml then may be a 'blip'.*	• Check CD4 count and clinical status. • If any indication of clinical and/or immunological failure then treatment failure is present. • If clinical condition is good and CD4 count increase is satisfactory then isolated virological failure is present.
*An HIV viral load 'blip' is a single 'detectable' result below 500 c/ml followed by an 'undetectable' result. It is due to normal biological and statistical variation and has no clinical significance.			

Table 13: Management of confirmed treatment failure

Steps	Action
Step 1	• Decide if treatment failure is likely (see 'Treatment Failure' above).
Step 2	• Decide what are the likely cause(s) of treatment failure: o Assess ART adherence: • Discuss ART adherence with patient in a non-judgmental manner. • Ask opinions of counselors and peer support workers. • Review additional information: clinic attendance, responses to adherence questions in patient file, pill counts. o Previous ART experience o Dosing (especially in children) o Drug interactions o Absorption (e.g. chronic diarrhea) o Interruption of ARV supply
Step 3	• Address causes of treatment failure: o Help with specific difficulties with adherence, e.g. additional support from HBC, reminder systems, etc o Change drugs/doses to avoid under-dosing or drug interactions.
Step 4	• Decide whether ART regimen should be changed in consultation with an expert.

15. Switching from first-line regimen to second-line therapy

- Switching to second-line therapy is an important and complicated decision that should only be made in consultation with an expert.

- The decision to switch therapy should not be based on a single laboratory result or clinical illness, but should take into account all available information including treatment history, adherence, clinical status, CD4 and HIV viral load results.

- Isolated virological failure is the most common reason for switching therapy in high income countries. It is unknown whether this is the optimal approach for people taking ARV in Cambodia, where second-line therapy is likely to be the last available treatment option. To ensure timely and effective second-line treatment, OI/ART clinicians should perform Viral Load Testing by referring blood samples to laboratory at NIPH or at the University of Health Sciences in Phnom Penh, With regards to some provincial referral hospitals, where clinicians are unable to make a decision on shifting from a first to second-line regimen, patients should be referred to NCHADS' CTAP Clinic .

- There is some data to suggest that clinical and immunological status can be maintained with an HIV viral load below 10,000 copies / mL, although drug resistance mutations will continue to accumulate.

Table 14: Standard Second-line ART regimen in Cambodia

Situation	Regimen
Standard second line ART regimen	**TDF+3TC+LPV/RTV (Kaletra)** or DDI +3TC + LPV/RTV (Kaletra)

References

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2. Recommendations for antiretroviral therapy in HIV infected adults and adolescents - 2002/2003: Brazilian Ministry of Health, 2002.

3. Fact sheets on antiretroviral drugs: SEARO, 2002.

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7. Guidelines for antiretroviral therapy in Zimbabwe: National Drug and Therapeutics Policy Advisory Committee, 2003.

8. Yeni P, Hammer S, Carpenter C, et al. Antiretroviral treatment for adult HIV infection in 2002: updated recommendations of the International AIDS Society - USA Panel. JAMA 2002; 288:222-235.

9. Antiretroviral Therapy for HIV Infection in adults and Adolescents in Resource-Limited-Settings: Towards Universal Access. Recommendations for a public health approach. 2006 version. World Health Organization

Annex 1: WHO staging system for HIV infection and disease in adults and adolescents

CLINICAL STAGE 1
Asymptomatic
Persistent generalized lymphadenopathy
CLINICAL STAGE 2
Moderate unexplained[a] weight loss (under 10% of presumed or measured body weight)[b]
Recurrent respiratory tract infections (sinusitis, tonsillitis, otitis media, pharyngitis)
Herpes zoster
Angular cheilitis
Recurrent oral ulceration
Papular pruritic eruptions
Seborrhoeic dermatitis
Fungal nail infections
CLINICAL STAGE 3
Unexplained[a] severe weight loss (over 10% of presumed or measured body weight)[b]
Unexplained[a] chronic diarrhoea for longer than one month
Unexplained[a] persistent fever (intermittent or constant for longer than one month)
Persistent oral candidiasis
Oral hairy leukoplakia
Pulmonary tuberculosis
Severe bacterial infections (e.g. pneumonia, empyema, pyomyositis, bone or joint infection, meningitis, bacteraemia)
Acute necrotizing ulcerative stomatitis, gingivitis or periodontitis
Unexplained[a] anaemia (below 8 g/dl), neutropenia (below 0.5 x 10^9/l) and/or chronic thrombocytopenia (below 50 x 10^9 /l)
CLINICAL STAGE 4[c]
HIV wasting syndrome
Pneumocystis pneumonia
Recurrent severe bacterial pneumonia
Chronic herpes simplex infection (orolabial, genital or anorectal of more than one month's duration or visceral at any site)
Oesophageal candidiasis (or candidiasis of trachea, bronchi or lungs)
Extrapulmonary tuberculosis
Kaposi sarcoma
Cytomegalovirus infection (retinitis or infection of other organs)
Central nervous system toxoplasmosis
HIV encephalopathy
Extrapulmonary cryptococcosis including meningitis
Disseminated non-tuberculous mycobacteria infection
Progressive multifocal leukoencephalopathy
Chronic cryptosporidiosis
Chronic isosporiasis
Disseminated mycosis (extrapulmonary histoplasmosis, coccidiomycosis)
Recurrent septicaemia (including non-typhoidal *Salmonella*)
Lymphoma (cerebral or B cell non-Hodgkin)
Invasive cervical carcinoma
Atypical disseminated leishmaniasis
Symptomatic HIV-associated nephropathy or HIV-associated cardiomyopathy

a Unexplained refers to where the condition is not explained by other conditions.

b Assessment of body weight among pregnant woman needs to consider the expected weight gain of pregnancy.

c Some additional specific conditions can also be included in regional classifications, such as the reactivation of American trypanosomiasis (meningoencephalitis and/or myocarditis) in the WHO Region of the Americas and penicilliosis in Asia.

Source: *Revised WHO clinical staging and immunological classification of HIV and case definition of HIV for surveillance*, 2006 (in press).

Annex 2: Antiretroviral medications and side effects

- Get to know the drugs. Spend time becoming familiar with each ARV drug, particularly the side effects it can cause and the management of these side effects.

- This section begins with two tables: the first (Table 15) provides a summary of some features of each ARV drug. The second table (Table 16) gives an overview of ARV side effects. Following the tables, each ARV drug is listed with discussion of its side effects.

- See also 'Principles of ARV therapy,' 'Diagnose and manage ARV side effects', Table 6, 'Management of specific groups' and 'Changing ARV therapy'.

Table 15 - ARV dosage, formulation, requirements and use in specific groups

Drug and drug class	Dose	Formulations	Cold storage needed for long term storage	Food effects	Renal and hepatic impairment*	Pregnancy (See page 22)	TB/HIV co-infection (See page 24)
NRTI							
Zidovudine (ZDV or AZT)	300mg (one tablet) twice per day	Capsule 100 mg, 250 mg; Tablet 300mg; Injection 10 mg/ml in 20 ml vial; Oral solution 10 mg/ml	No	None	No change necessary	Preferred	Preferred
Stavudine (d4T)	30mg (one capsule) twice per day	Capsule 15 mg, 20 mg, 30 mg,; Oral solution 1mg/ml	Only for reconstituted oral solution	None	CrCl 10-50ml/min: halve each dose	Yes (not combined with ddI)	Acceptable, but increased risk of neuropathy
Lamivudine (3TC)	150mg (one tablet) twice per day	Tablet 150mg; Oral solution 10mg/ml	No	None	CrCl 10-50ml/min: 150mg daily	Preferred	Preferred
Didanosine (ddI)	>60kg: 400mg (one EC capsule) once per day <60kg: 125mg twice per day or 250mg (one EC capsule) once per day	Tablet 25 mg, 50mg, 100 mg, 150 mg, 200 mg;Oral solution 10mg/ml; EC Capsule 125mg, 200mg, 250mg, 400mg	No	Take at least 30 minutes before or 2 hours after meal	CrCl 10-50ml/min: Normal dose, but only once per day	Yes (not combined with d4T)	Acceptable, but increased risk of neuropathy
Abacavir (ABC)	300mg (one tablet) twice per day	Tablet 300mg; Oral solution 20mg/ml	No	None	No change necessary	No	Yes, but may be difficult to diagnose ABC hypersensitivity in this setting
NtRTI							
Tenofovir (TFV or TDF)	300mg (one tablet) once per day	Tablet 300mg	No	Take with meal	Do not give to patients with renal impairment (CrCl < 50ml/min)	No	No

NNRTI							
Nevirapine (NVP)	200mg (one tablet) once per day for two weeks, then 200mg (one tablet) twice per day	Tablet 200 mg; Oral suspension 10mg/ml	No	None	Renal: No change necessary Hepatic: avoid	Preferred	Avoid if possible as overlapping toxicity and dosing is not clear
Efavirenz (EFV)	600mg (one capsule) once per day	Capsule 50 mg, 100 mg, 200 mg, 600mg; Syrup 30mg/ml	No	Avoid taking with high fat meal	Renal: no change necessary Hepatic: consider alternative drug	No	Preferred
PI							
Nelfinavir (NFV)	1250mg (five tablets) twice per day	Tablet 250 mg; Powder 50 mg/g	No	Take with food; at least a light meal	No data	Preferred	No
Indinavir + ritonavir (IDV/r)	400mg/100mg (two capsules) twice per day	IDV Capsule 100 mg, 200 mg, 333 mg, 400 mg; RTV Capsule 100mg; oral solution 80mg/ml	Only for RTV capsules: stable for 30 days at room temperature	None	Renal: avoid if possible. No change necessary in dose. Hepatic: avoid	Yes	No
Lopinavir + ritonavir (LPV/r)	400mg/100mg (three capsules) twice per day (co-formulated)	Tablet 200mg + 50mg Capsule 133.3 mg + 33.3 mg; Oral solution, 80mg/ml + 20mg/ml	Yes; stable for 2 months at room temperature	Take with food	Renal : no data Hepatic : Avoid	No	No
Saquinavir + ritonavir (SQV/r)	1000mg/100mg (six capsules) twice per day	SQV Capsule (hard gel (HGC) or soft gel (SGC) filled) 200 mg ; RTV Capsule 100mg; Oral solution 80mg/ml	Only for SQV SGC (stable for 3 months) and RTV capsules (stable for 30 days) at	None	Renal : no data Hepatic : avoid	Yes	Yes

			room temperature				

Combination							
Zidovudine + Lamivudine (AZT + 3TC)	300mg/150mg (one tablet) twice per day		No	None	Use individual formulations if CrCl < 50ml/min	Preferred	Preferred
Stavudine + Lamivudine (d4T + 3TC)	30mg/150mg (one tablet) twice per day		No	None	Use individual formulations if CrCl < 50ml/min	Yes	Acceptable, but increased risk of neuropathy
Stavudine + Lamivudine + Nevirapine (d4T + 3TC + NVP)	After two week induction, OR 30mg/150mg/200mg (one tablet) twice per day		No	None	Renal : Use individual formulations if CrCl < 50ml/min Hepatic : Avoid	Yes	Avoid if possible as overlapping toxicity, increased risk of neuropathy and dosing is not clear
Zidovudine + Lamivudine + Nevirapine (AZT + 3TC + NVP)	After two week induction, 300mg/150mg//200mg (one tablet) twice per day		No	None	Renal : Use individual formulations if CrCl < 50ml/min Hepatic : Avoid	Preferred	Avoid if possible as overlapping toxicity and dosing is not clear
Zidovudine + Lamivudine + Abacavir (AZT + 3TC + ABC)	300mg/150mg//300mg (one tablet) twice per day		No	None	Use individual formulations if CrCl < 50ml/min	No	Yes, but may be difficult to diagnose ABC hypersensitivity in this setting

*ESRF is not considered in these recommendations. For specific information on patients with CrCl<10ml/min or on dialysis refer to reference texts.

Table 16: Management of major side effects of ARV

Side effect	Major ARV causes	Presentation	Prevention	Management
Abdominal pain	Hepatitis: d4T, NVP, EFV, RTV Pancreatitis: ddI, d4T	Abdominal pain	Check ALT (and hepatitis serology) at baseline. Avoid these agents if risks for hepatitis or pancreatitis	Check amylase and ALT. Consider abdominal ultrasound. See 'Hepatitis' or 'Pancreatitis' or 'Lactic Acidosis'
Anaemia	AZT	Weakness, lethargy, dizziness	Check CBC at baseline. Avoid AZT if Hb<100g/l.	Hb>80g/l: check for OI. Check Hb again in 2-4 weeks Hb<80g/l: cease AZT
Central Nervous System effects*	EFV	Central Nervous System symptoms*	Consider using other ARV if any mental illness or harmful substance use	Mild symptoms: continue EFV, monitor, give EFV at night Severe symptoms: cease EFV
Diarrhea	ddI, NFV, RTV	Diarrhea	Nil	Check for other causes. Give symptomatic treatment. Cease drug if severe or persistent
Headache	AZT, EFV	Headache	Nil	Check for other causes. Cease drug if severe or persistent
Hepatitis	d4T, NVP, EFV, full dose RTV	Lethargy, nausea, vomiting, abdominal pain, jaundice	Check ALT (+/- hepatitis serology) at baseline. Avoid these drugs if risks for hepatitis	ALT/AST<5xULN: check ALT/AST again in 2-4 weeks. ALT/AST>5xULN: cease drug
Hyperbilirubinaemia	IDV	Nil	Nil	Usually nil required
Hyperglycaemia/ diabetes	All PIs	Lethargy, thirst, polyuria, polydipsia	Avoid PIs if risks for diabetes	If diabetes develops, start metformin. Increase medications as needed. If unable to be controlled cease PI
Hyperlipidaemia	All PIs, especially RTV	Nil	Avoid PIs if risks for hyperlipidaemia	Continue PI and add anti-lipid therapy. If unable to be controlled cease PI (see page 41)
Hypersensitivity syndrome	ABC, NVP	Rash (esp.NVP), fever, hepatitis, eosinophilia	Nil	Cease drug and never restart as restarting may be fatal.
Kidney stones	IDV	Loin pain, haematuria	Maintain hydration. Drink >1.5l/day	Cease IDV. Hydration and analgesia. Restart IDV unless repeated episodes
Lactic acidosis	AZT, d4T, ddI	Lethargy, nausea, vomiting, diarrhea and dyspnoea.	Avoid d4T +ddI (especially during pregnancy)	See Table 11 (page 34)
Lipodystrophy	All (especially AZT, d4T and ddI for lipoatrophy and PIs for central fat accumulation)	Peripheral fat wasting, central obesity, visceral fat accumulation, 'buffalo hump' and breast enlargement	Consider using drugs other than d4T and PIs	Cease d4T or AZT
Myopathy	AZT	Proximal muscle wasting and weakness	Nil	Cease AZT
Nausea/vomiting	AZT, ddI, RTV, LPV/r	Nausea/vomiting	Nil	Check for other cause. Give symptomatic treatment. Cease drug if severe or persistent

Neutropenia	AZT	Nil	Check CBC at baseline. Avoid AZT if neutrophil count<1x10^6/l. Check CBC at 4 weeks.	Neutrophil count>1x10^6/l: check CBC again in 2-4 weeks. Neutrophil count<1x10^6/l: cease AZT
Pancreatitis	ddI, d4T	Nausea, vomiting, abdominal pain	Avoid ddI, d4T if risks for pancreatitis	Check amylase. Cease drug if amylase > 500 or severe or persistent symptoms.
Peripheral neuropathy	d4T, ddI	Peripheral numbness, tingling, pain or weakness	Consider using drugs other than d4T, ddI	Cease drug unless mild and stable
Rash	NVP (also ABC)	Erythema, bullae, mucosal ulceration	Two week low dose initiation of NVP	ABC: cease drug and never restart as restarting may be fatal NVP: cease drug if severe, bullae, mucosal involvement or fever
Teratogenicity	EFV	Congenital defects	Avoid EFV if risk of pregnancy	Cease EFV

*Includes dizziness, headache, insomnia, depression, impaired concentration, agitation, nightmares, sleepiness, severe depression, suicidal ideation, mania and delusions.

Annex 2.1: Nucleoside Reverse Transcriptase Inhibitors (NRTIs)

Class side effect: Lactic acidosis/hepatic toxicity

- Asymptomatic elevations in blood lactate level are common in people taking NRTIs. They are not predictive of lactic acidosis.

- Symptomatic elevations in blood lactate are less common and true lactic acidosis is rare, but often fatal (See Table 11 below).

- Risk factors for lactic acidosis are the use of NRTIs, in particular d4T and/or ddI. Other possible risk factors are female sex, high body mass index, pregnancy and acquired riboflavin and thiamine deficiency.

- Symptoms include weakness, lethargy, nausea, vomiting, diarrhea and dyspnoea.

- Laboratory features are acidosis with an increased anion gap and raised lactate, AST/ALT, creatinine kinase, lactate dehydrogenase and amylase. If measurement of

lactate is not available a constellation of the above symptoms with increased anion gap acidosis and raised AST/ALT is suggestive of lactic acidosis.

- Cease all NRTIs as soon as suspected. Treatment is supportive (fluid replacement, bicarbonate and respiratory support if available).

- Restart ARV without d4T or ddI and preferably without AZT or 3TC, particularly if the episode was life threatening. For example, combine ABC or TDF with a NNRTI and a PI.

- Raised ALT or AST occurs in 5-15% of people taking NRTIs, but is symptomatic in less than 1%.

Table 17: Features and management of hyperlactataemia

Grade	Lactate (mmol/l)	Frequency (%)	Management		Mortality (%)
			No symptoms	Symptoms	
Severe	>10	0.1	Cease ARV	Cease ARV	80
Moderate	5-10	1	Observe	Exclude other causes and cease ARV	0
Mild	2-5	5	Observe and look for other metabolic complications	Exclude other causes and consider ceasing ARV	0

Class side effect: Lipoatrophy

- Lipoatrophy is part of the lipodystrophy syndrome. It seems to be more closely associated with the use of NRTIs, particularly d4T and AZT. It results in reduction in peripheral fat, particularly of the face, arms, legs and buttocks, resulting in a characteristic appearance with prominent cheek bones and prominent veins on the limbs.

- Lipoatrophy is common and generally becomes apparent after one to two years of therapy. Studies investigating the role of switching drugs in the management of lipoatrophy have generally had disappointing results. Switching d4T or AZT to ABC has shown very slow reversal of peripheral lipoatrophy. Drug treatment is currently being studied.

Zidovudine (AZT)

- Anemia and neutropenia are the major side effects. The overall rate of these side effects is 5-10%, but is much higher in people with advanced HIV disease. Management is either by dose reduction (if not severe), transfusion and/or discontinuation.

- Headache, nausea and fatigue occur in approximately 5-10% of people, but usually resolve over a few weeks.

- Myopathy with myalgia, proximal weakness and wasting can occur and is usually reversible with cessation of AZT.

Stavudine (d4T)

- The major side effect of d4T is peripheral neuropathy. It is more common and more severe with higher dose, longer duration of use, more advanced HIV disease and with the use of other neurotoxic drugs, particularly ddI. Symptoms usually gradually resolve over a few weeks after cessation of d4T, but can persist and cause wasting.

- d4T is more likely to cause the NRTI class-specific side effects than other NRTIs: lactic acidosis, hepatic toxicity and lipoatrophy.

- d4T can also cause pancreatitis. Again, this is more common when d4T is given together with ddI.

- A Guillain-Barre like syndrome has occurred with d4T. If there are any signs consistent with this syndrome, for example motor weakness, then d4T should be ceased.

Lamivudine (3TC)

- 3TC and FDC are well tolerated with very few side effects.

- Uncommon, but reported side effects are headache, fatigue, nausea, vomiting, diarrhea, pancreatitis, peripheral neuropathy, neutropenia and hepatic toxicity.

Didanosine (ddI)

- The major side effects of ddI are peripheral neuropathy and pancreatitis. Peripheral neuropathy occurs in approximately 6-15% of users. The risk is probably increased if d4T is given at the same time. Symptoms usually resolve over a few weeks after cessation, but can persist and cause wasting.

- Pancreatitis occurs in approximately 1-7% of users and is fatal in 1%. Risk factors are use of higher doses, high alcohol consumption, severe obesity, hypertriglyceridaemia, gallstones and the use of other drugs that can cause pancreatitis such as d4T. ddI must be ceased if pancreatitis occurs.

- ddI can also cause diarrhea, nausea, vomiting or abdominal pain in about 5-18% of users.

Abacavir (ABC)

- The major side effect of ABC is hypersensitivity syndrome. It occurs in 3-5% of users and can be fatal. The average time to onset is one week after ABC is started and over 90% of cases will occur in the first six weeks, but it can occur at any time.

- Typical symptoms are constitutional and include:

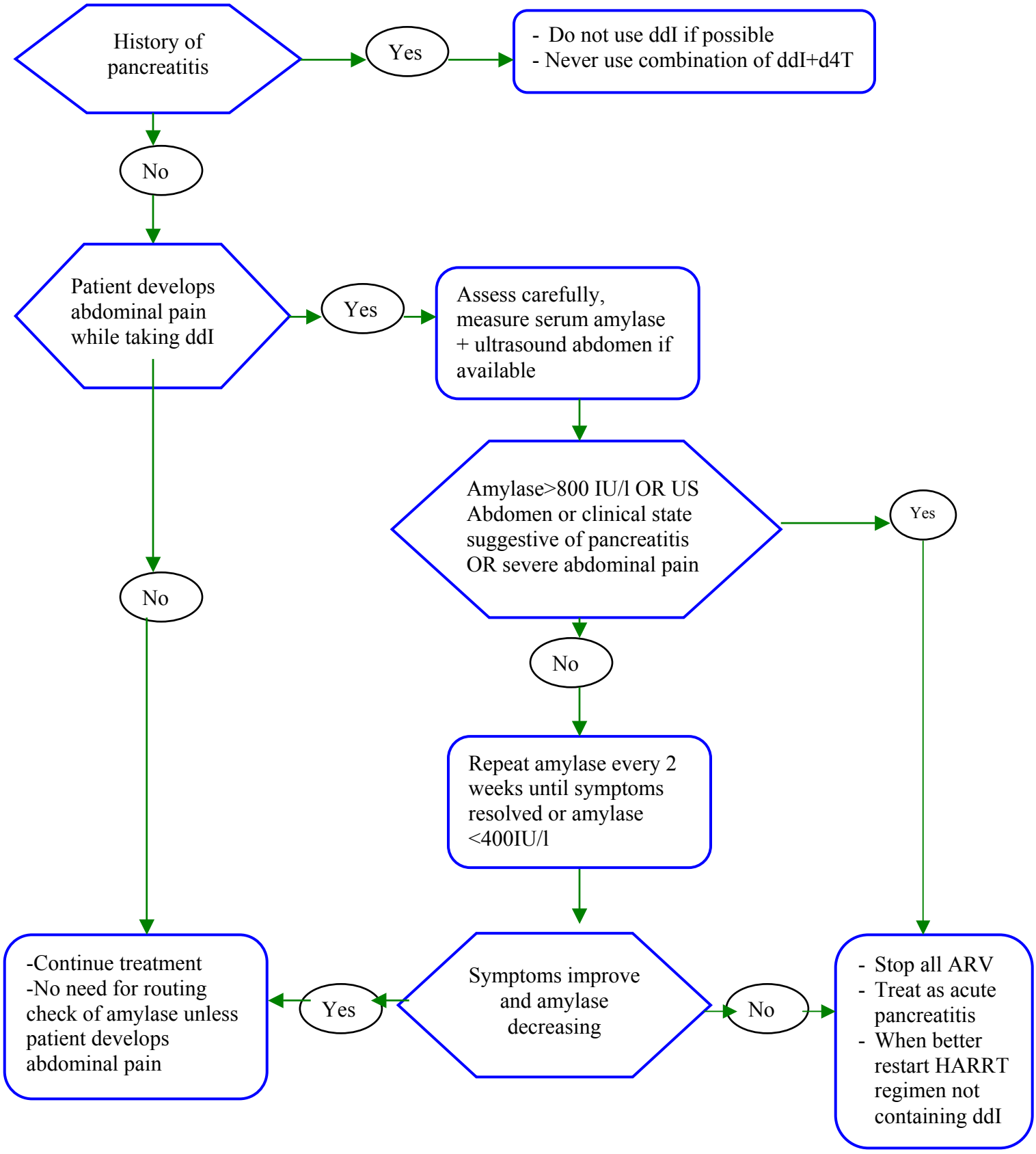
- Fever is the most common feature.
- Rash is common, but not prominent.
- Gastrointestinal: nausea, vomiting, diarrhea, abdominal pain
- Respiratory: pharyngitis, cough, dyspnoea
- Generalized arthralgia, myalgia, headache, malaise

- Examination may show fever, rash, lymphadenopathy and mucosal ulceration. Investigation may reveal elevated liver enzymes, creatinine kinase, creatinine and thrombocytopenia.

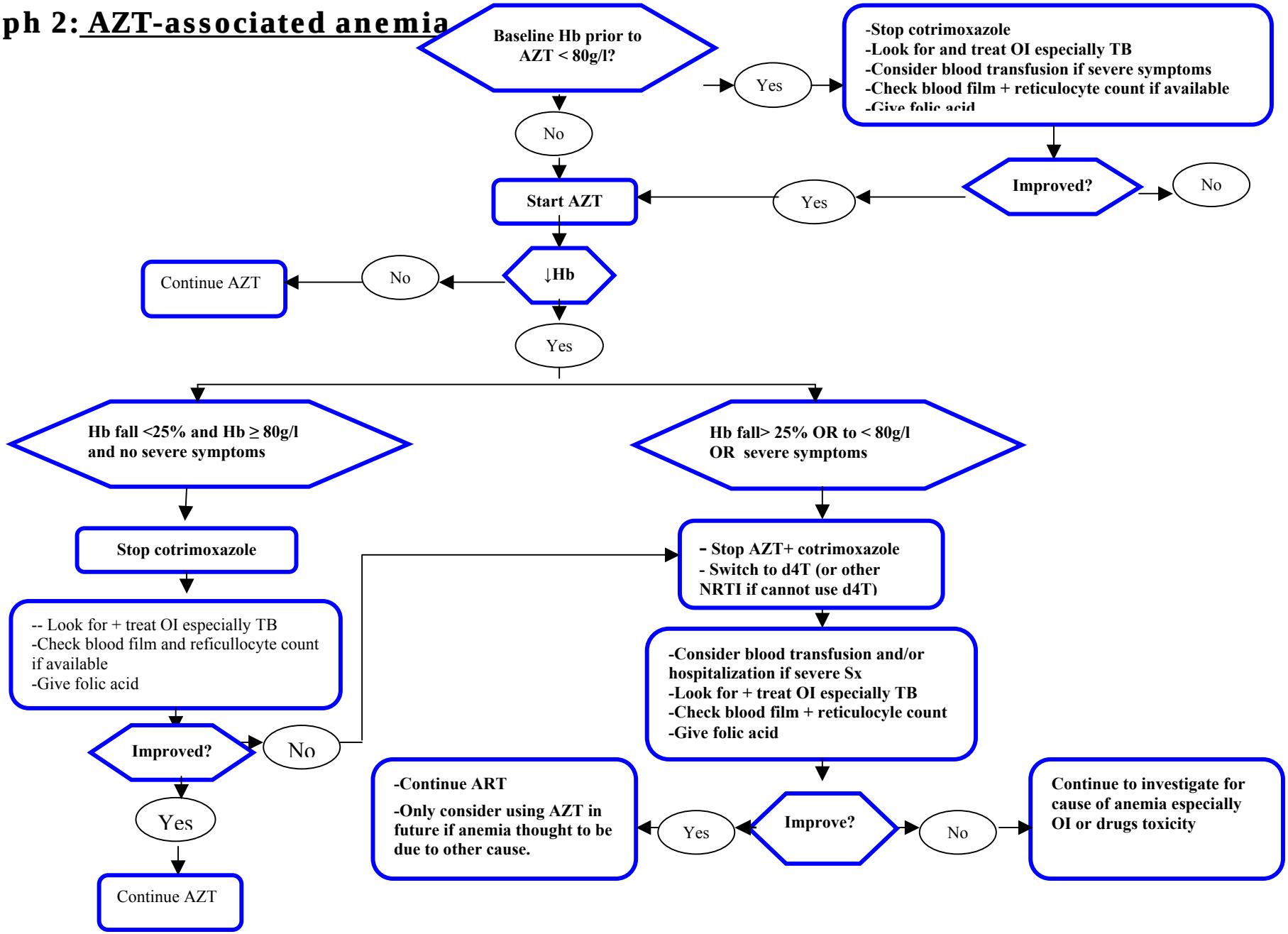
- Differentiation from other illnesses can be extremely difficult. Most characteristic of ABC hypersensitivity are:
  - Involvement of multiple organ systems, for example gastrointestinal and respiratory symptoms
  - Acute onset of symptoms
  - Worsening of symptoms as further doses of ABC are taken

- People taking ABC should be intensively counseled regarding hypersensitivity syndrome and advised to report any symptoms promptly. If hypersensitivity is suspected by a health care provider, ABC should be ceased and never restarted, because re-challenge can result in rapidly fatal reactions. Management is supportive. There is no evidence that steroids are of benefit.

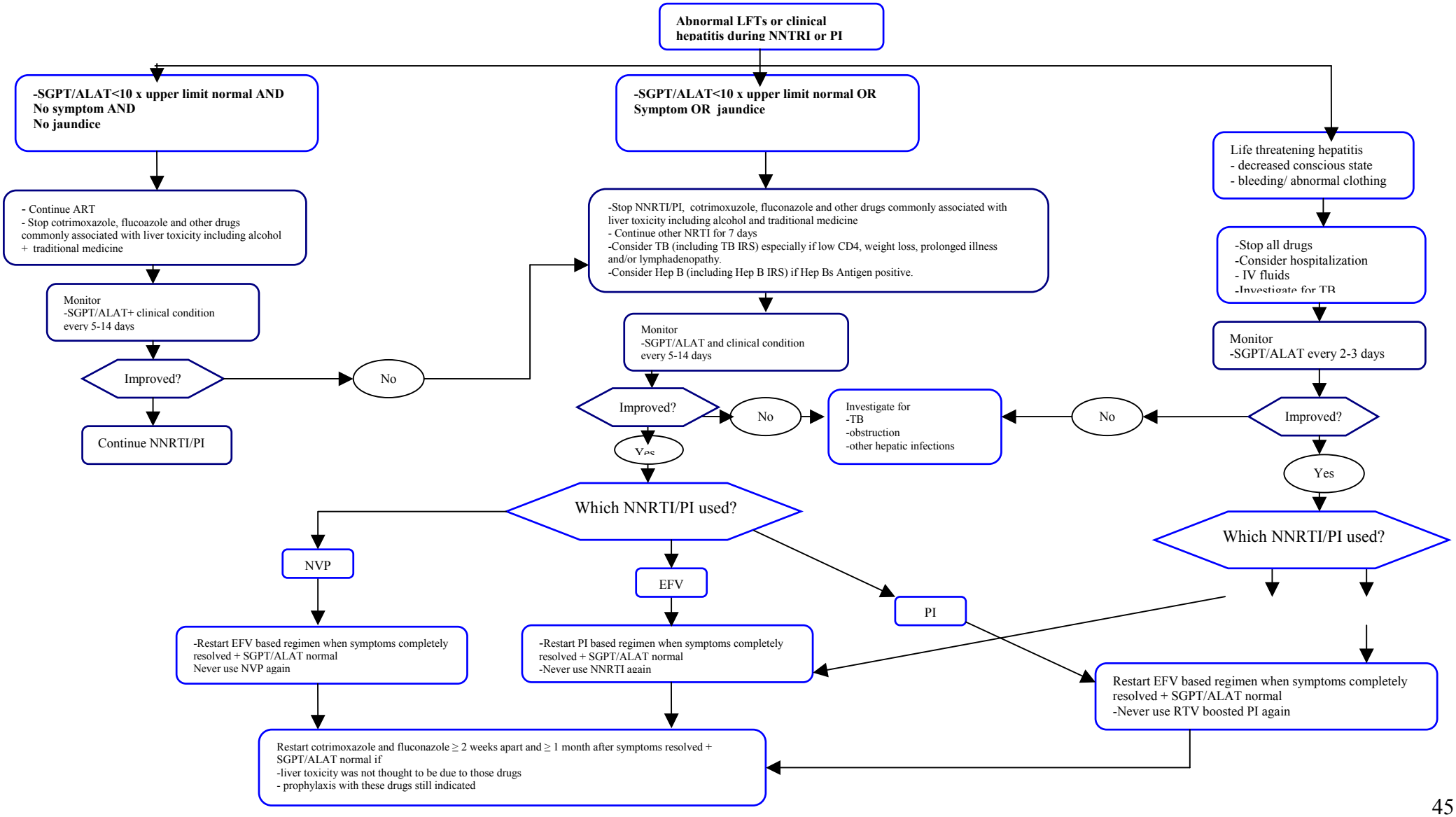
Graph 1: ddI associated pancreatitis:



Graph 2: AZT-associated anemia



Graph 3: ART-Associated liver toxicity



Annex 2.2: Nucleotide Reverse Transcriptase Inhibitors | (NtRTIs)

Tenofovir (TDF)

- TDF is very well tolerated with few side effects. Nausea, vomiting and diarrhea can occur and are usually mild. There have also been case reports of Fanconi syndrome and renal impairment, but definite causation has not been established.

Annex 2.3: Non-Nucleoside Reverse Transcriptase | Inhibitors (NNRTIs)

Class side effect: Rash and hepatitis

- Rash can occur with both NVP and EFV, but severe rash including Stevens-Johnson syndrome has only been described for NVP.

- There does not seem to be cross-reactivity for rash between NVP and EFV, so EFV can be used if rash has occurred with NVP and vice versa. However, if the NVP rash is severe or associated with mucosal involvement, EFV should not be used.

- Hepatitis can occur with both NVP and EFV, but is more common with NVP (See Table 11). It is probably safe to use the other agent if hepatitis occurred with NVP or EFV, except if the hepatitis was severe or life threatening.

Table18 : NNRTI side effects (Grade 3/4) in the 2NN study

Percentages	NVP 400mg once/d	NVP 200mg twice/d	EFV 600mg once/d
Clinical hepatotoxicity	1.4	2.1	0.3
Laboratory hepatotoxicity	13.2	7.8	4.5
Central nervous system toxicity	1.8	4.9	6.5
Discontinuation due to toxicity	24.1	21.2	15.5

Nevirapine (NVP)

- The major side effects of NVP are rash and hepatitis.

- Rash occurs in about 17% of users, is serious enough to result in discontinuation in 6-8% and develops into Stevens Johnson syndrome or toxic epidermal necrolysis in 0.3%.

- The most common time for development of rash is in the first two to four weeks. It is usually erythematous, maculopapular, confluent and most prominent on the body and arms. Fever, myalgia, hepatitis and eosinophilia can also occur.

- If mild to moderate rash without other symptoms or mucosal involvement occurs, NVP can be continued with careful observation. During the two-week low dose NVP initiation, it is preferable to cease all ARV if rash occurs. Restart ARV including NVP once the rash has settled. Do not increase the dose of NVP until the rash has resolved. Steroids are not useful.

- If any of the following are present, NVP should be permanently ceased and neither NVP or EFV given in the future:
  - Severe rash
  - Rash with bullae or target lesions
  - Mucosal involvement
  - Hypersensitivity syndrome: fever, myalgia, hepatitis and eosinophilia.

- Hepatitis can occur alone or with rash and/or hypersensitivity syndrome. Abnormal liver function tests occur in about 15% and clinical hepatitis in about 1-5%. Rarely, hepatic failure and death can occur. About two thirds of cases occur in the first 3 months of use, but can occur at any time.

- Risk factors for NVP associated hepatitis are abnormal liver function tests at baseline, excess consumption of alcohol, older age, female sex, co-infection with hepatitis B or C and a higher CD4 count.

- Symptoms are generally non-specific: malaise, anorexia, nausea, vomiting. It should be noted that abdominal pain and jaundice do not always occur. As detailed above, hepatitis may occur as part of a hypersensitivity syndrome with rash, fever, myalgia and eosinophilia.

- NVP should be permanently discontinued if NVP associated hepatitis is diagnosed. EFV can be used if the hepatitis was not severe or life threatening.

Efavirenz (EFV)

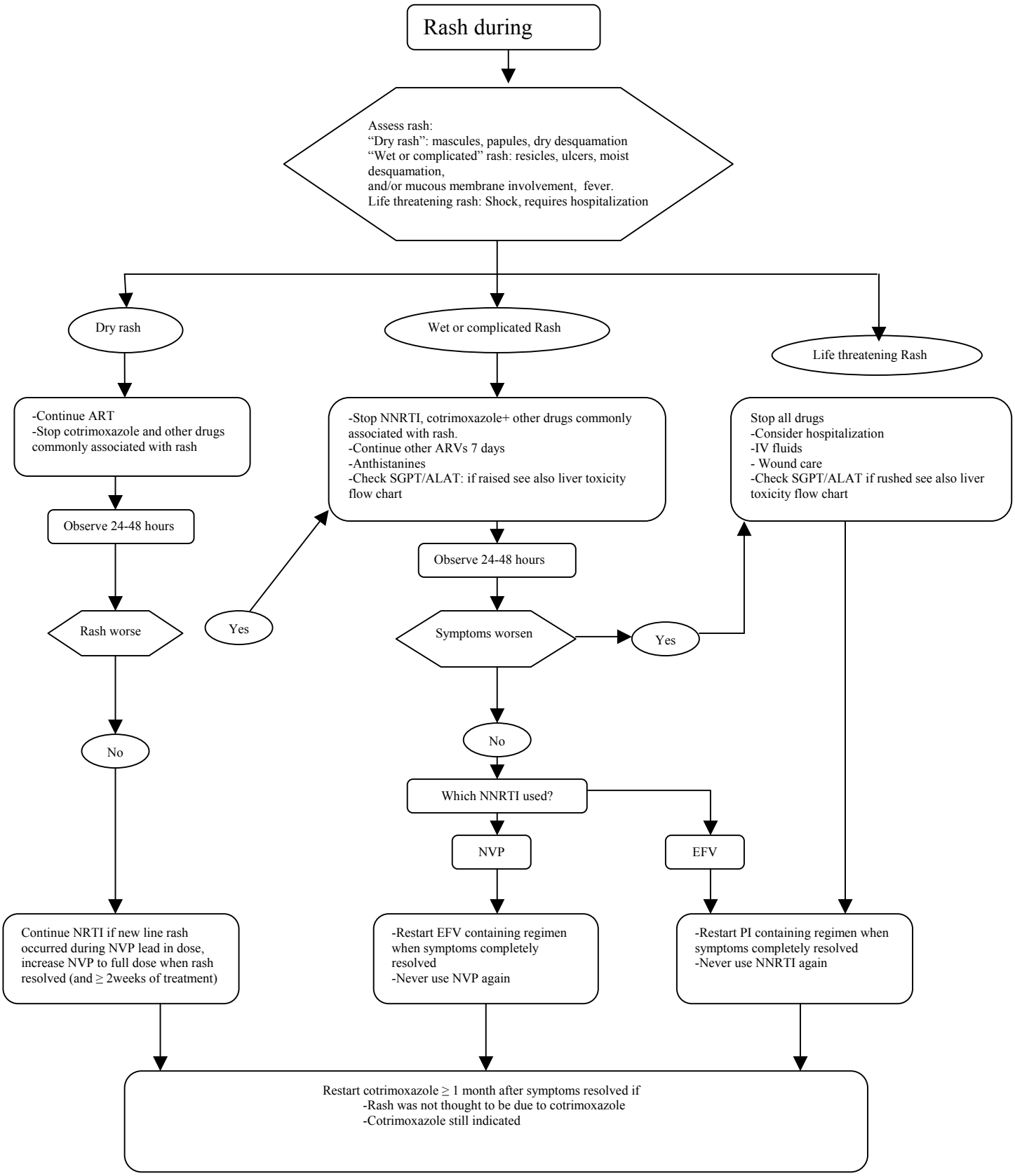
- The major side effects of EFV affect the central nervous system.

- These side effects occur in 30-50% of users and include dizziness, headache, insomnia, depression, impaired concentration, agitation, vivid dreams, nightmares and sleepiness. These symptoms usually settle after a couple of weeks. Less than 2% of users develop major psychiatric symptoms such as severe depression, suicidal ideation, mania and delusions. These usually occur in those with a previous history of mental illness or substance use disorders.

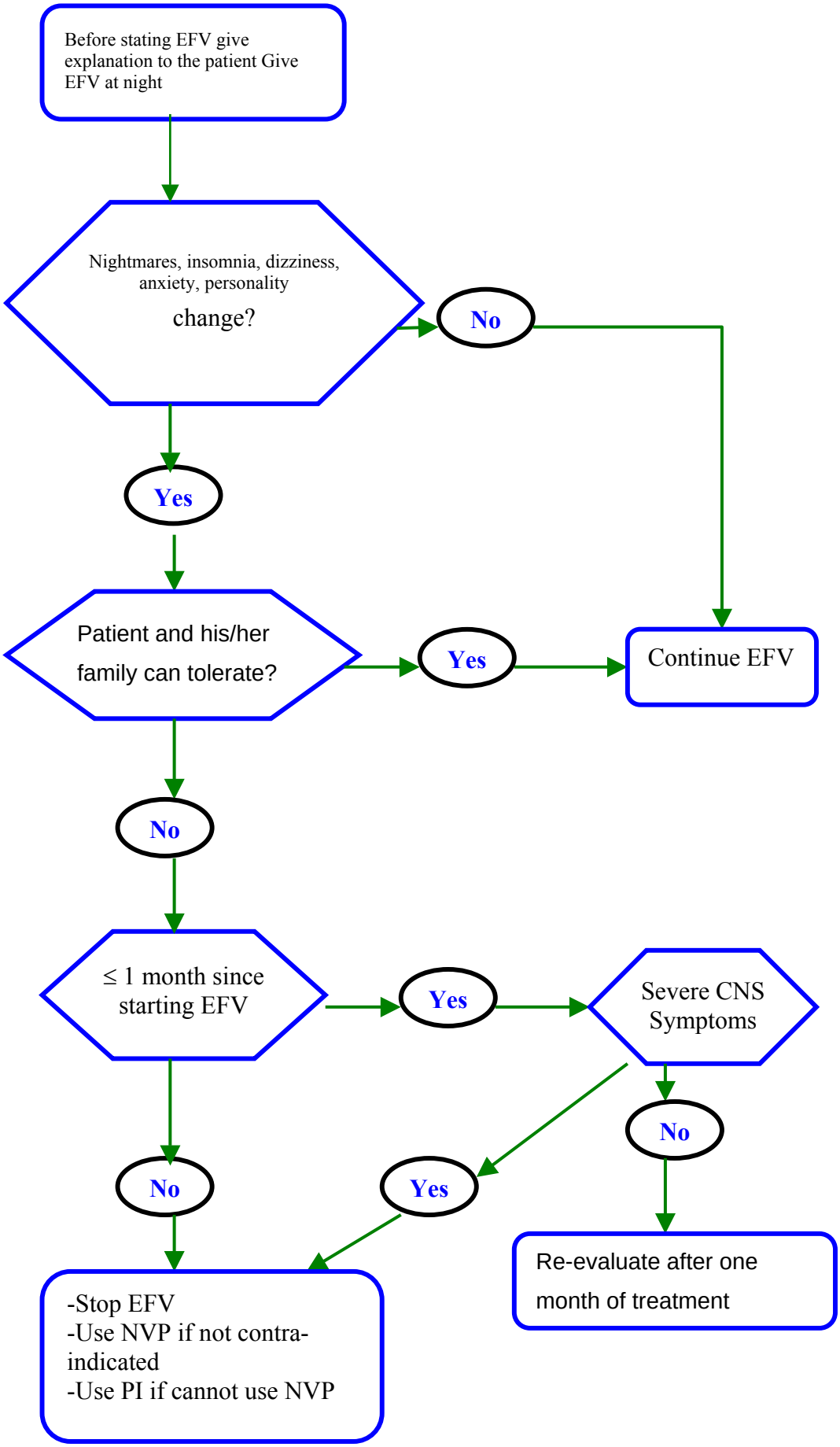
- If symptoms are mild, EFV can usually be continued and may be given at nighttime to reduce their effect. If severe, EFV should be permanently ceased.

- Other side effects of EFV are rash and hepatitis (See 'Class-specific side effect: rash and hepatitis', page 37). It is also teratogenic and should not be given during pregnancy, particularly during the first trimester.

Graph 4: NNRTI-associated rash



Graph 5: EFV-associated CNS symptoms



Annex 2.4: Protease Inhibitors (PIs)

Class side effect: metabolic complications

- All PIs can cause a group of metabolic complications that include lipodystrophy, insulin resistance and diabetes, hyperlipidaemia.

Class side effect: lipodystrophy

- This syndrome includes peripheral lipoatrophy, which is more closely associated with the use of NRTIs particularly d4T, and central fat accumulation (central obesity, visceral fat accumulation, 'buffalo hump' and breast enlargement), which is more closely associated with the use of PIs. This complication of PI therapy often coexists with other metabolic complications.

- Lipodystrophy occurs in the majority of people taking a combination of NRTIs and a PI. It generally becomes apparent after one to two years of therapy. Studies investigating the role of switching drugs in the management of lipodystrophy have generally had disappointing results. Switching the PI to a non-PI drug has not been shown to provide substantial benefit. Switching d4T or AZT to ABC has shown very slow reversal of peripheral lipoatrophy. Drug treatment of lipodystrophy is currently being studied.

Class side effect: insulin resistance and diabetes

- Insulin resistance occurs in up to 40% of PI users, hyperglycaemia in 3-17% and clinical diabetes in 1%. Onset is usually a few months after starting therapy.

- When symptoms occur they are those of diabetes: lethargy, thirst, polyuria and polydipsia.

- PIs can usually be continued together with drug management of hyperglycaemia/diabetes. Studies are ongoing, but metformin is probably the best first line treatment. If severe or difficult to control, PIs should be ceased. Hyperglycaemia usually, but not always, resolves after cessation.

Class side effect: hyperlipidaemia

- All PI drugs can cause elevation of triglycerides and cholesterol, but RTV seems to cause the most marked elevations. Whether these elevations increase the risk of cardiovascular disease is not yet clear.

- Drug therapy for hyperlipidaemia should be initiated at standard thresholds. Isolated increase in LDL-cholesterol should be treated with a statin, preferably pravastatin because this drug has less interactions with PIs. Start at low doses and watch carefully for the development of myopathy. Isolated increase in triglycerides should be treated with a fibrate, for example gemfibrozil or fenofibrate. Combined increases in LDL-cholesterol

and triglycerides can be treated with either a statin or a fibrate. Data available to date suggests that drug therapy is not effective at lowering either LDL-cholesterol or triglycerides to generally accepted targets. Combined therapy with a statin and a fibrate may be more effective, but may also increase the risk of myopathy. Severe elevations in lipids are best managed by switching the PI to a drug from another class, although the lipid abnormalities may persist despite this.

Class side effect: hepatitis

- PIs, particularly RTV, can cause elevation of liver enzymes and clinical hepatitis at any time during treatment by an unknown mechanism.

- Risk factors include elevated liver function tests at baseline, excess alcohol intake, hepatitis B and/or C co-infection and the use of other hepatotoxic drugs including d4T.

- Minor elevations in liver enzymes can be observed and the PI continued. If more marked elevations or clinical hepatitis occur the PI should be permanently discontinued.

Class side effect: bone disorders

- Regimens containing PIs seem to be associated with an increased risk for osteopenia, osteoporosis and avascular necrosis.

Nelfinavir (NFV)

- NFV is relatively well tolerated with the only significant side effect being gastrointestinal upset. Diarrhea commonly occurs soon after starting NFV and usually, but not always, resolves over a few weeks. Abdominal pain and flatulence also occur.

Indinavir/ritonavir (IDV/r)

- The major side effect of IDV is kidney stones (nephrolithiasis), which occurs in about 10% of users. It presents with typical flank pain and haematuria. Management is supportive with hydration and analgesia. IDV (and therefore all ARV) should be ceased for a few days until symptoms settle. Unless repeated episodes have occurred, IDV can be restarted with close attention to ongoing hydration. All people taking IDV should be advised to drink at least 1.5 liters of fluid per day.

- Asymptomatic indirect hyperbilirubinaemia is seen in about 10% of users, usually in the first few weeks of treatment. Clinical jaundice or elevations in transaminases are rare and so usually no specific management is required.

- IDV can also cause retinoid-like side effects: alopecia, dry skin, dry lips and ingrown nails.

- About 3% of people taking IDV develop esophageal reflux.

- The ritonavir component can cause peri-oral and peripheral paraesthesia. This is not dangerous, but can be severe enough to require change of drug.

Lopinavir/ritonavir (LPV/r)

- The major side effects of this combination are probably due to the RTV component: diarrhea and hyperlipidaemia. Pancreatitis has also occurred, possibly secondary to hypertriglyceridaemia. Paraethesia can occur.

Saquinavir/ritonavir (SQV/r)

- The major side effects of this combination are likely to be more associated with the RTV component: nausea, diarrhea, abdominal pain, headache, paraesthesia and liver toxicity.

Annex 3: Important ARV drug interactions

- There are many complicated interactions between ARVs and other drugs.
- Table 19 gives an overview of major drug interactions. There are many more drug interactions that are not listed in this table. Always check reference texts for interactions before prescribing new drugs.

Table 19: Important ARV drug interactions

Interacting drug	NVP	EFV	NFV	IDV/r	LPV/r	SQV/r
Ketoconazole	X	?	OK			
Rifampicin	Use with caution	EFV 800mg/d	X	X	X	Give both drugs at full dose
Rifabutin	OK	RBT 450-600 mg/d	RBT 150mg/d NFV 1000mg tds			RBT 250mg 2-3/week
Clarithromycin	OK	X	?		?	
Oral contraceptive[1]	X	X	X	X	X	X
Methadone	Increase methadone	Increase methadone	Increase methadone	Increase methadone	Increase methadone	Increase methadone
'Statins'[2]	?	?	X		X	X
Other drugs that should not be co-administered	Garlic supplements	Astemizole Terfenadine Cisapride Midazolam Triazolam Ergotamine Dihydro-ergotamine Garlic supplements	Astemizole Terfenadine Cisapride Midazolam Triazolam Ergotamine Dihydro-ergotamine Garlic supplements	Astemizole Terfenadine Cisapride Midazolam Ergotamine Dihydro-ergotamine Garlic supplements Flecanide Pimozide	Astemizole Terfenadine Cisapride Midazolam Ergotamine Dihydro-ergotamine Garlic supplements Flecanide Pimozide	Astemizole Terfenadine Cisapride Midazolam Ergotamine Dihydro-ergotamine Garlic supplements Flecanide Pimozide
Miscellaneous	Can lower steroid levels	Monitor warfarin if co-administered				

[1]Additional or alternative methods of contraception should be used.
[2]Pravastatin can be used.

Annex 4: Karnofsky Performance Scale

Table 20: Karnofsky performance scale

Level of function	Score	Description
Able to carry on normal activities and to work; no special care needed.	**100**	Normal no complaints; no evidence of disease.
	90	Able to carry on normal activity; minor signs or symptoms of disease.
	80	Normal activity with effort; some signs or symptoms of disease.
Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed.	**70**	Cares for self; unable to carry on normal activity or to do active work.
	60	Requires occasional assistance, but is able to care for most of his personal needs.
	50	Requires considerable assistance and frequent medical care.
Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly.	**40**	Disabled; requires special care and assistance.
	30	Severely disabled; hospital admission is indicated although death not imminent.
	20	Very sick; hospital admission necessary; active supportive treatment necessary.
	10	Moribund; fatal processes progressing rapidly.
	0	Dead