Kingdom of Cambodia
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Ministry of Health

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

2nd Revision in January, 2012

National Center for HIV/AIDS, Dermatology and STD

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Preface

Cambodia is one among the successful countries in the Western Pacific Region in the response to the HIV epidemic by reducing the HIV prevalence among people aged 15-49 years-old from 2.4% in 1998 to 0.8 % in 2010. It is estimated that there are 75,131 people who are living with HIV, of whom 50,927 people are in need for antiretroviral therapy,

Since its launching in 2003, the Comprehensive Continuum of Care (CoC) Framework for PLHIV, Cambodia has achieved the universal access target for HIV treatment, with over 90 percent of adults and children in need receiving antiretroviral therapy (ART), with 56 for Adult OI/ART sites, and 33 Pediatrician OI/ART sites delivering HIV care and ART to 45,647 patients on ART at the end of the third quarter 2011.

Noting the above developments and to build Cambodia's readiness to achieve universal coverage and the national target of 95% coverage (NSP III target), Cambodia is intent on harmonizing ARV guidelines with those set out by the WHO. In many regards, Cambodia has anticipated WHO recommendations and already implemented appropriate changes to its current ARV program. In 2010, Cambodia expanded antiretroviral therapy to all asymptomatic HIV infected individuals including pregnant women with CD4 counts less than 350 cells/mm^3 and persons with HIV/TB regardless of CD4 count.

I would like to congratulate NCHADS and all development partners who were actively participated in revising these important guidelines. These guidelines for the use of antiretrovirals are therefore timely and essential. Ministry of Health has officially approved for the use of Antiretroviral Therapy in Adults and Adolescents and hopes that all health care workers involved in the CoC framework for PLHIV, and implement these national guidelines.

Phnom Penh, 27 / 01 / 2012
Minister for Health

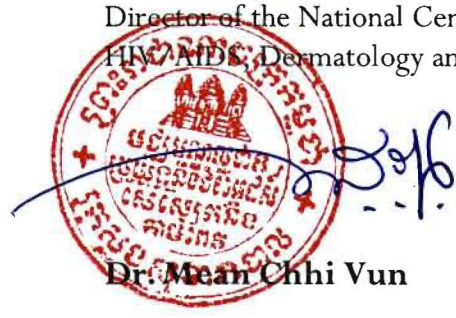
Dr. MAM BUNHENG
MINISTER OF HEALTH

Acknowledgement

The National Center for HIV/AIDS, Dermatology and STD (NCHADS) invested a significant amount of time and resources in the preparation of the original ARV treatment guidelines in 2003 and revisions in 2007 and now 2011. The revised 2011 guidelines not only stem from recent WHO recommendations but also build on the vast experience acquired over the course of the past ten years by NCHADS and all its partners, including government, NGOs and donors.

As with the 1st and 2nd editions of the National ARV Guidelines, we wish to thank all those who have contributed to the development of this document. In particular, we wish to record our special thanks to the following groups and individuals for their efforts in revising the original document, including the Staff of the AIDS Care Unit of the National Center of HIV/AIDS, Dermatology and STD, Members of the AIDS Care Subcommittee on Antiretroviral Therapy, the World Health Organization (WHO), including consultant Dr. Suresh Rangarajan, US-CDC, Clinton Health Access Initiative, FHI, and Dr. Benjamin Westley, Brown University (U.S.A), Physician participants of the Consensus Workshop on Adult Antiretroviral Therapy and the Prevention and Treatment of Opportunistic Infections in Cambodia.

Phnom Penh, 25/01/2012
Director of the National Center for
HIV/AIDS, Dermatology and STD



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Abbreviations

3TC	Lamivudine
ABC	Abacavir
AIDS	Acquired Immunodeficiency Syndrome
ALT	Alanine Transaminase
AST	Aspartate Transaminase
ART	Antiretroviral therapy
ARV	Antiretroviral drug(s)
AZT	Zidovudine
BS	Birth Spacing
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
FDC	Fixed Dose Combination
HBV	Hepatitis B virus
HGC	Hard Gelatin Capsules
HIV	Human Immunodeficiency Virus
IPT	Isoniazid Preventive Therapy
LDH	Lactate Dehydrogenase
LDL	Low-Density Lipoprotein
LPV	Lopinavir
LPV/RTV	Lopinavir/Ritonavir

MMM	Modul Mith Chouy Mith
MTCT	Mother to Child Transmission
NNRTI	Non-Nucleoside Reverse Transcriptase Inhibitor
NRTI	Nucleoside Reverse Transcriptase Inhibitor
NVP	Nevirapine
OHL	Oral Hairy Leukoplakia
OI	HIV related Opportunistic Infection
PCP	*Pneumocystis carinii* pneumonia
PEP	Post Exposure Prophylaxis
PLHIV	Person/People Living with HIV
PI	Protease Inhibitor
PITC	Provider Initiated Testing and Counseling
PMTCT	Prevention of Mother to Child Transmission
PPE	Papular Pruritic Eruption
PTB	Pulmonary Tuberculosis
R	Ritonavir (when given in association with other PIs for boosted dosing)
RLS	Resource Limited Settings
RNA	Ribonucleic Acid
RTV	Ritonavir (when given alone or with other PIs for boosted dosing)
SGC	Soft Gelatin Capsules
STI	Sexually Transmitted Infection
TB	Tuberculosis
TDF	Tenofovir
TST	Tuberculin Skin Test
ULN	Upper Limit of Normal
VCCT	Voluntary Centers for Counseling and Testing
VDRL	Venereal Diseases Reference Laboratory (refers to a test for syphilis)
WHO	World Health Organization

1. Summary

In July of 2010, the WHO released a revised Antiretroviral Therapy for HIV Infection in Adults and Adolescents Guideline. This revision reflects new available evidence from well-resourced and resource limited settings on ART initiation, ARV regimens, ARV toxicity, ART with active TB and/or chronic hepatitis, laboratory monitoring, and identification and management of treatment failure.

In supporting their recommendations, the WHO panel used a systematic and clear approach to evaluating evidence and making recommendations using GRADE methodology that incorporates cost effectiveness, acceptability, and feasibility. However, although WHO recommendations include phasing-out the use of d4T in ART, this is currently not feasible in Cambodia. Over the coming years, NCHADS with support from the Global AIDS Fund and local and international partners to expand the availability of affordable alternatives to d4T and reconsider this issue in the future.

This revision of the National Guidelines for the use of Antiretroviral Therapy in Adults and Adolescents remains an integral component in the national response to providing high-quality care to PLHIV in Cambodia. It is written primarily for health care workers who are involved in the care of adults and adolescents (>14 years) living with HIV/AIDS.

It aims to provide a clear explanation of the basics of ARV therapy. It should be used as an introduction and a reference and should not substitute for comprehensive training in the administration and monitoring of ART. Similarly it does not seek to address the complex operational requirements of comprehensive HIV care in general, nor of ARV provision in particular. These questions are addressed in the "Continuum of care for people living with HIV/AIDS operational framework" and will be further addressed in future publications. The reader is also referred to national guidelines and standard operating procedures for detailed information and recommendations regarding the Continuity of Care programmatic framework involving PLHIV and the provider community including PITC and VCCT, SOP for 3Is, psychosocial and social support, OI prevention and treatment, PMTCT, and post-exposure prophylaxis.

These 2011 guidelines include a number of updates pertaining to relevant aspects of ART including:

Broader access to ART

The current guidelines expand ART eligibility to all patients with Stage 3 WHO clinical stage in addition to Stage IV WHO clinical stage and PLHIV with active TB regardless of CD4 count. Asymptomatic individuals will continue to be eligible for ART at CD4 counts less than 350 cells/mm^3.

Emphasis on earlier initiation of ART

ART should be initiated within 2 weeks of clinical presentation. These guidelines have detailed important steps during the first three visits to quickly initiate ART to promote immunological restoration and treat and prevent opportunistic infection to reduce morbidity and mortality associated with uncontrolled HIV infection (see section 4).

Incorporation of SOP for 3Is in clinical assessment

At each visit, this guideline incorporates important screening and action plans for identified case positive TB symptoms as set forth by the SOP for 3Is (see section 4).

Changes to preventative therapies for opportunistic infections

These guidelines have been revised in parallel with the 1st edition of Guidelines for Prevention and Treatment of Opportunistic Infections in Adults and Adolescent (2011). Changes incorporated in this guideline reflect the importance of quickly beginning IPT per the SOP for 3Is, cotrimoxazole prophylaxis for prevention of PCP and toxoplasmosis, and fluconazole for prevention of cryptococcal disease (see section 4).

More specific first line regimens

As mentioned, d4t and 3TC continues to be the first-line NRTIs in the standard regimen. Additional detail has been included on appropriate changes to regimens based on HBV status and during pregnancy depending on trimester of ART initiation.

Early detection of treatment failure using expanded viral load testing strategy

Eligibility for viral load testing will be significantly expanded during the implementation of these guidelines. A stepwise algorithm for identifying and addressing clinical and immunological failure is clarified. Based on clinical and immunological failure, providers should follow the described targeted viral load testing to assess treatment failure. In addition, over the coming years, routine viral load testing will be implemented for persons on ART for more than 2 years. These guidelines detail important steps provides should take when screening for treatment failure with routine viral load testing (see section 8).

Revision of second-line ART regimens

Second line ART regimens have been revised to reflect the limited ARV options available to Cambodia, ARV toxicity, and common viral resistance patterns encountered with first-line regimens. ddI and 3TC have been replaced by ABC and 3TC as the alternative NRTIs for second-line therapy. Providers should dispense their current stock of ddI and then switch patients to TDF or ABC regimens (see section 9).

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 3 main classes. Two of the classes inhibit reverse transcriptase and one class inhibits protease:

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

Cambodia currently does not have access to newly developed more durable to resistance NNRTIs such as Etravirine and PIs such as Darunavir. In addition, the use of three more classes of ARV drugs has shown activity against HIV, including entry (Maviroc), integrase (Raltegravir), and maturation (Bevirimet) inhibitors. However, at present they are not widely available in resource limited settings (RLS) and some 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)
  Tenofovir (TDF)

- NNRTI Nevirapine (NVP)
  Efavirenz (EFV)

- PI Lopinavir and low dose Ritonavir (LPV/r)
  Low dose Ritonavir (RTV/r)

PIs should always be administered together with Ritonavir. 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 of the primary PI. The preferred boosted protease inhibitor in Cambodia is LPV/r, which is formulated in a heat stable tablet.

Most ARV drugs recommended for use in Cambodia are available as fixed dose combinations, which should be used whenever possible to minimize the number of necessary tablets and maximize adherenece. Drugs used in Cambodia must be prequalified by WHO and currently include:

- 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 to prevent and treat opportunistic infections
- Improved quality of life
- Reduction of HIV related morbidity and mortality
- Minimize adverse events, and chronic conditions from long-term ARV therapy
- 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 combination antiretroviral therapy (ART) and are most effective when given early in the course of the disease.

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, which is measured by the CD4 count.

As immune function is restored, the risk of HIV-associated illness decreases. In individuals and populations using ART the risk of illness and death is dramatically reduced. However, 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 on ART.

ART is not a cure for HIV. It suppresses viral replication, but does not eradicate the virus. If ART 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 ART 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.

Moreover, early detection of treatment failure is essential. If left untreated resistant viruses can accumulate more genetic mutations that make them less susceptible to other ARV drugs and be transmitted to others (see Table 1).

Table 1: How is HIV transmitted?

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 can be spread to healthcare workers through penetration of skin by infected needles or prolonged or large quantity exposure of contaminated blood to mucosal surfaces and non-intact skin
Untreated individuals with acute primary HIV are at significant risk for transmitting HIV due to high circulating virus
Someone can be infected with HIV and be well for many years but still transmit HIV
Genital ulcers and sexually transmitted diseases increase risk of transmission
Abstinence from sexual intercourse and condom use as well as not reusing needles are the most effective methods to reduce transmission of the virus
HIV cannot be transmitted by normal social contact, kissing, sharing food or by insects

4. Starting antiretroviral therapy

4.1 Confirm HIV infection

Consider HIV under the following circumstances:

- Risk behavior (high risk sexual behavior, IV or subcutaneous drug use)
- Pregnancy
- Sexually transmitted infection
- Tuberculosis (TB)
- Repeated bacterial infections
- Wasting (>10% loss of expected body weight)
- Clinical suggestion of other opportunistic infections: neurological signs with fever including any meningitis and focal deficits, acute pneumonia, suggestive cutaneous signs (herpes zoster, oral thrush, PPE, etc.).
- Clinical suggestion of acute primary HIV including fever, malaise, muscle pain, lymphadenopathy, pharyngitis, and rash in an otherwise previously healthy adult

All health care workers should follow provider initiated testing and counseling (PITC) guidelines and provide information on the importance of HIV testing and refer patients with their consent to VCCT (please see separate PITC and VCCT guidelines including Policy Strategy and Guidelines for HIV Counseling and Testing, 2007). In addition to behavior modification and HIV education, patients receive screening and confirmatory rapid antibody testing to identify infection before referral to an appropriate AIDS care and treatment site.

4.2 First Doctor Visit (day of presentation)

- Collect relevant demographic data on patient and family members
- Confirm HIV test results, time of detection, place of testing
- Assess current medical history including recent symptoms and treatment
- TB symptom screening per 3Is Strategy (see Table 2) and follow suspected TB algorithm in case of positive signs
- Assess past medical history including:
  - TB and TB treatment (time of diagnosis and treatment, place of treatment, treatment regimen and outcome)
  - History of chronic lymphadenopathy, recurrent upper respiratory infections or pneumonia, OIs, sexually transmitted and other diseases
  - Obstetric, gynecological history, use of contraceptive methods
  - Previous ART exposure including regimen and duration or PMTCT

- Previous OI prophylaxis treatment including INH, cotrimoxazole, and fluconazole and associated side affects, if any
- Drug allergies including antibiotics (such as cotrimoxazole)
- Current medications

Table 2: TB screening per 3Is Strategy

TB Symptom Screening	Responses	Management
In the last 4 weeks: 1) fever, anytime of any duration 2) cough, anytime of any duration 3) Two weeks or more of drenching night sweats	No Symptoms	Start INH prophylaxis*
	1 or more symptoms	TB clinical assessment, AFB Smears x 3 (plus culture if available), and CXR per 3Is Strategy

* Do not start INH until confirm that AST/ALT<3 ULN, no active alcohol consumption, and no previous adverse reaction to INH. Place TST at this visit if available at OI/ART site (see Standard Operating Procedures (SOP) for Implementing the 3Is in Continuum of Care Setting, 2010)

- Assess social history including:
  - marital status and occupation
  - alcohol use and drug use
  - cigarette smoking
  - high risk sexual behaviors
  - other family members with HIV infection including testing and ART history, and HIV disclosure status with family members
  - functional status using Karnofsky Performance Scale (see Annex 6)
- Physical Exam
  - vital signs, weight, height
  - general condition and mental status
  - visual acuity and neurological signs
  - ear-nose-throat conditions
  - heart and circulation
  - respiratory function
  - abdominal findings including enlarged liver, spleen, and lymph nodes
  - peripheral lymphadenopathy
  - mucocutaneous manifestations
- Investigate, assess, and treat current illnesses as clinically indicated (see National Guidelines for Prevention and Treatment of Opportunistic

Infections among HIV-exposed and HIV-infected Adults and Adolescents, 2011)

- Start IPT prophylaxis if TB screening or TB clinical assessment negative pending results of AST/ALT (see SOP for 3Is and National Guidelines for Prevention and Treatment of Opportunistic Infections among HIV-exposed and HIV-infected Adults and Adolescents, 2011)
- If positive for active TB, start cotrimoxazole prophylaxis
- Assess current WHO clinical stage (see Annex 1)
  - If stage III or IV begin immediate adherence counseling, start cotrimoxazole prophylaxis, and START ART as soon as possible (see Table 6 for timing to initiate ART based on clinical conditions).
- Perform routine investigations
  - CD4, CBC, AST/ALT

IF CLINICAL STAGE III OR IV
START ART AS SOON AS POSSIBLE (SEE TABLE 6)
DO NOT WAIT FOR BASELINE CD4 COUNT RESULTS

During this visit providers should also focus on providing holistic support to patients as provision of drugs alone is not sufficient support to PLHIV. This includes:

- HIV education and counseling
- 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 (see National Guidelines for Prevention and Treatment of Opportunistic Infections among Adults and Adolescents, 2011).
- Social and financial support can help as PLHIV 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 ART into the comprehensive care approach).

4.3 Second Doctor Visit (before1 week)

- Continue investigation and treatment of current illnesses
- TB symptom screening per 3Is Strategy (see Table 2) and follow suspected TB algorithm in case of positive signs
- Check results of routine investigations and assess eligibility for ART (Table 3)
- Perform routine pre-ART tests CD4, CBC, AST/ALT (Table 4) if not already completed
- Initiate OI prophylaxis (Table 5) if not already started.

Table 3: Criteria to start ART*

WHO Clinical Stage	Adults without TB, but with HIV/HBV co-infection and pregnant women	
2	<350 cells/mm^3	Adults with TB coinfection
3	TREAT ALL	
4	TREAT ALL	

***After appropriate counseling and preparation**

Table 4: Recommended laboratory monitoring prior to ART

Laboratory test	Essential	Optional
HIV antibody	X	
CD4 count	X	
AST / ALT	X	
Pregnancy test	Essential if using EFV	
CBC	X	
Chest X-ray	If required for TB assessment	If clinically indicated
HIV viral load	Not required	Not required
Creatinine	Essential if use TDF	If clinically indicated
Phosphate		if using TDF
Amylase		if clinically indicated
Lipids		if on d4T, EFV, or PI
Hepatitis B Surface Ag and Antibody	if AST/ALT>3 or if clinically indicated	if AST/ALT<3 or if clinically indicated

DO NOT DELAY ART IF UNABLE TO COMPLETE ESSENTIAL LABS WITHIN TWO WEEKS

Prophylaxis of opportunistic infection is an integrated part of a package of comprehensive care for PLHIV. All PLHIV should have access to information and educational materials regarding prophylactic therapy including isoniazid, cotrimoxazole, and fluconazole prophylaxis. The table below summarizes when and what OI prophylaxis to start. For additional details on OI prophylaxis including dosing, desensitization, and side effects, please refer to separate National Guidelines for the Prevention and Treatment of Opportunistic Infections among Adult and Adolescent, 2011.

Table 5: Summary of OI prophylaxis for PLHIV

Prophylaxis	Eligibility	Recommended Dosing and Duration
Isoniazid/Pyridoxine (vitamin B6)	All patients with HIV without active TB regardless of CD4 count including pregnant women regardless of trimester*	INH 5 mg/kg to a maximum of 300 mg/day (Patient weighing < 40 kg should be given 200 mg) **and** Pyridoxine (vitamin B6) 50 mg/day for 6 months
Cotrimoxazole	All PLHIV with CD4 count less than 200 OR with Stage 3 or 4 HIV disease regardless of CD4 count including pregnant women regardless of trimester	1 double strength (DS; TMP-160mg, SMX-800mg) tablet daily or 2 single (SS; TMP-80mg, SMX-400mg) tablets daily. Adults should receive cotrimoxazole prophylaxis until asymptomatic and CD4 counts are above 200 on 2 separate measurements at least >6 months apart
Fluconazole	All PLHIV with CD4 count of less than 100 cells/mm^3. Except pregnant women in first trimester	100 mg orally once per day (200 mg per day if previous cryptococcal infection). Adults should receive fluconazole prophylaxis until CD4 counts are above 100 on 2 separate measurements at least >6 months apart

* Please refer to SOP on 3Is for eligibility, initiation, and monitoring for IPT. In areas where tuberculosis skin testing is available, patients with positive skin tests are eligible for 36 months of INH prophylaxis, whereas, patients with a negative skin test are not eligible for IPT.

4.4 Third Doctor Visit (before 2 weeks)

- Continue investigation and treatment of current illnesses
- Ask about new symptoms and side affects of prophylactic medicines
- TB Screening per 3Is Strategy (see Table 2) and follow the TB diagnosis algorithm in case positive symptoms

- Measure vital signs and weight and perform targeted physical exam based on current illness and symptoms
- Reassess clinical staging
- Check results of routine pre-ART examinations
- Proceed to dispense OI prophylaxis if not given ARV yet.
- Check understanding of HIV and ART. The success of ART is dependent on the understanding and commitment of the individual taking ARV. It is not easy to predict who will have difficulties with adherence.
- Decide if ART can be started.
- Select ART regimen, **START ART**, and schedule appropriate follow-up (2 weeks).
- Make appointment to follow-up of the treatment with ART after one month. For patients who uses ARVs for a while, high understanding on treatment, stable health conditions, the appointment can be made every two or three months, but it cannot be more than three months.

4.5 Starting ART in the setting of an active opportunistic infection

A significant body of recent research has demonstrated that early initiation of ART in the setting of an opportunistic infection improves morbidity and mortality. It is now recommended that ART should be initiated **within two weeks of treatment of opportunistic infections** that have traditionally been associated with immune reconstitution syndrome (see section 6.7), with the exception of TB in which ART should be started immediately after two weeks of starting TB treatment.

ART improves immune function and will support the resolution of the active OI more quickly and prevents the occurrence of new OIs. For certain active OIs such as cryptosporidiosis, progressive multifocal leukoencephalopathy, CMV infections, and Kaposi sarcoma, ART also offers the only available effective therapy and should be promptly initiated.

Even in cases of severe immunosuppression and high viral loads, it is preferable to initiate ART before the OI is fully controlled. Table 6 can assist providers in deciding when to initiate ART in the setting of some common OIs:

Table 6: Timing of ART initiation in setting of active OIs

Opportunistic Infection	Time between start of treatment for OI and initiation of ART
Tuberculosis	Start ART immediately after two weeks of TB treatment initiation phase.
Disseminated mycobacterium avium-intracellulare complex	Start ART as soon as possible
PCP	Start ART as soon as possible, once no reaction to cotrimoxazole identified
Toxoplasmosis	Start ART as soon as possible
Hepatitis B and C	Start ART as soon as possible
Cytomegalovirus	Start ART as soon as possible
Varicella-Zoster	Start ART as soon as possible
Histoplasmosis	Start ART as soon as possible after induction with amphotericin B
Penicillium	Start ART as soon as possible after induction with amphotericin B
Cryptococcus*	Start ART as soon as possible after induction with amphotericin B
Progressive multifocal leukoencephalopathy	Start ART as soon as possible
Kaposi Sarcoma	Start ART as soon as possible, in absence of other treatment

*ART may be delayed in cases of uncontrolled intracranial pressure associated with cryptococcal meningitis. ART should be initiated if patient has access to neurological monitoring and emergent lumbar puncture.

The simultaneous use of ART with treatment of OIs other than TB and induction with amphotericin is not limited by difficult drug interactions and should be feasible in most situations (see Annex 3). If IRIS is identified, individual symptoms can typically be managed without discontinuation of ART in the most cases.

There are a however number of challenges that accompany initiation and monitoring of ART during treatment of an active OI:

- Patients might not fully absorb ARVs and have subtherapeutic blood levels that leads to viral resistance
- Renal and hepatic function may be affected by OIs and affect ARV blood levels
- Progression of symptoms of the OI may be confused with new OI or IRIS
- Symptoms of IRIS may take weeks or months to resolve

5. What to First-line Regimen to Start?

The decision of first line regimen is primarily driven by the associated toxicities including anemia, peripheral neuropathy, TB, HBV, and pregnancy status of infected individuals.

In the current guidelines, NVP continues to be a favored first-line NNRTI. When starting NVP in any individual, a lower dose NVP should used during the first two weeks of therapy to avoid overdosage and allow the induction of cytochrome P450 metabolism of NVP. This includes patients with prior ART therapy more that was discontinued more than two weeks prior to reinitiation of ART. If the patient does not have side effects to NVP initiation, the NVP dose can be increased to twice daily. If the patient has a reaction to NVP, it may be necessary to stop the drug immediately depending on the severity of side effects (see section Table 8 on NVP initial dosing and section 6.5 on how to diagnose and manage ARV side affects).

During the upcoming years, d4T may be phased-out of first line regimens due to associated toxicities with extended therapy. However, the current guidelines will continue to recommend d4T and 3TC as the preferred NRTIs in first-line regimens until a steady supply of affordable alternatives medications can be guaranteed in the future.

Standard dosing and adjustments for renal and hepatic function for all ARVs are available for your reference in Annex 2 and Table 18.

5.1 First-line ARV regimens

Table 7 is a summary of standard first-line regimens for HIV infected ART eligible individuals

Table 7: Standard ARV first-line regimen

Situation	Regimen
Standard first-line ART regimen	**d4T + 3TC + NVP**
Alternatives due to ARV side effects	
Neuropathy	AZT + 3TC + NVP
Neuropathy and anemia	Seek expert advice
AST/ALT > 5 times upper limit of normal	d4T + 3TC + EFV
Patients with HIV/TB Coinfection	
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	AZT + 3TC +NVP (start in 1st trimester) AZT + 3TC + EFV (start in 2nd/3rd trimesters)
TB treatment and contraindication or intolerance to EFV	d4T + 3TC + NVP
Patients with HIV/HBV Coinfection	
History of HBV now immune (surface antigen negative)	d4T + 3TC + NVP
Chronic inactive HBV (see section 5.3)	d4T + 3TC + NVP
Chronic active HBV (see section 5.3)	TDF+ 3TC + EFV
Pregnant Women	
Pregnancy	AZT + 3TC + NVP
Pregnancy with anemia (1st Trimester of pregnancy)	d4T + 3TC + NVP
Pregnancy with anemia and neuropathy (1st Trimester of pregnancy)	TDF + 3TC + NVP
Pregnancy with AST/ALT > 5 times upper limit of normal (1st trimester of pregnancy)	TDF + 3TC+ AZT (during 1st trimester) then switch to AZT+3TC+EFV (after 1st trimester)
Pregnancy with AST/ALT > 5 times upper limit of normal (2nd and 3rd trimesters of pregnancy)	AZT + 3TC + EFV
Pregnancy with TB	See above

Previous ART experience	Seek expert advice

Expert advice
Expert advice includes NCHADS training team, ARV subcommittee members, and international consultants. All initial inquiries should be directed to the OI/ART designated NCHADS trainer.

Initiating NVP as part of ART

NVP initiation can be associated with side effects including rash and heptatitis. In order to minimize for these events, lower-lead in dosing in patients is recommended. The dose can safely be increased after two weeks due to increased ability of the liver to metabolize NVP.

If a patient is being switched from an EFV based regimen or on TB therapy and received at least two weeks of Rifampicin, the ability of the liver to metabolize NVP has already increased and no lead in dosing of NVP is needed. See Table 8 for lead in dosing strategies

Dosing of NVP during the first two weeks can be challenging as it often requires the use of individual tablets, two drug fixed combinations, and three drug fixed dose combinations. If no reactions or adverse events are observed, NVP can be administered at full dose in fixed dose combinations (FDC) after two weeks. Fixed dosed combinations are always preferred for long-term ART therapy due to decreased pill burden and improved adherence.

The following two drug FDCs are available in Cambodia:

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

The following three drug FDCs are available in Cambodia:

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

Table 8 outlines recommended strategies based on ARV and TB treatment history for dosing when initiating NVP based regimens.

Table 8: Lead in dosing of NVP based on ART and TB treatment history*

ARV and TB treatment history	Weeks 0 – 2		After 2 Weeks
ARV Naïve	AM	NVP 200 mg tablet and other NRTIs as part of two drug FDC (AZT+3TC or d4T+3TC)	NVP as part of three drug FDC Twice Daily
	PM	Two drug FDC (AZT+3TC or d4T+3TC)	
Switching from current use of EFV	NVP as part of three drug FDC Twice Daily		NVP as part of three drug FDC Twice Daily
On TB treatment and received at least two weeks of rifampicin	NVP as part of three drug FDC Twice Daily		NVP as part of three drug FDC Twice Daily

*If to drug or three drug FDCs are not available for the selected ARV regimen, use individual ARV tablet.

In addition to proper dosing during the initiation of NVP, patients on NVP should be monitored for hepatitis during the initial 4 months of NVP therapy. Liver function should be monitored every 2 weeks for the first month and each month for the second, third, and fourth months of therapy with NVP use. If AST/ALT>5 x upper limit in non-pregnant individuals algorithm in Figure 3. If AST/ALT >2x upper limit of normal in pregnant individuals, seek expert advice on management of NVP induced hepatitis during pregnancy.

5.2 People coinfected with TB

- Start TB therapy immediately after diagnosis of TB with cotrimoxazole prophylaxis regardless of CD4 count.

- ART should be started immediately after two weeks of TB therapy. This short time period is adequate to assess for adverse reactions to TB drugs and cotrimoxazole prophylaxis while improving morbidity and mortality.

The choice of ART regimen is complicated by the use of rifampicin throughout TB treatment. Rifampicin primarily interacts with NNRTI and PI but not NRTI drug classes. The interactions between rifampicin and the NNRTI and PI classes are due to the fact that rifampicin stimulates the activity of the cytochrome P450 (3A4) liver enzyme system which metabolizes lopinavir, nevirapine, and to a lesser extent, efavirenz. Rifampicin decreases the blood levels of these drugs. PIs and NNRTIs can

also modify this same enzyme system activity and lead to altered blood levels of rifampicin. The potential drug-drug interactions may result in failure of ART or TB treatment or an increased risk of drug toxicity.

Although, Rifampicin reduces EFV drug levels, most studies suggest that trough levels remain in the therapeutic ranges with regular efavirenz dosing. For this reason, Efavirenz without dosing adjustments is the NNRTI of choice for use in patients receiving rifampicin-based TB therapy. EFV should not be used during the first trimester of pregnancy.

If LPV/r based regimen is used, the dose of the LPV or ritonavir must be increased to keep LPV drug levels therapeutic. Ritonavir specifically inhibits the CYP 3A4 enzyme, and for this reason is used to "boost" blood levels of lopinavir when given together. LPV/r should be given at a dose of 400mg/400mg (two 200/50 mg and three 100mg RTVtablets) twice daily. If small dose RTV tablets are not available, providers should double the standard daily dose of LPV/r and administer 800 mg/200 mg twice daily.

NVP is not typically used during TB therapy due to overlapping hepatoxicity with standard TB therapy due to interactions with Rifampicin. However, if the patient has contraindication or intolerance to EFV, a NVP based regimen may be used during TB therapy. NVP should be administered at the standard dose without the low dose lead in period (because the hepatic cytochrome P450 system is already induced by Rifampicin) and liver function monitored every two weeks during initiation phase with Rifampicin TB treatment. If providers have questions or a patient has worsening liver function, an expert should be consulted.

In addition, providers should also refer to Annex 3 as well as National Guidelines for the Management of HIV/TB Coinfection (2009) and associated updates to assess for interactions between ARVs and drugs used for opportunistic infections and TB treatment.

After TB therapy, all patients who started EFV based regimens with TB treatment should switch to NVP based regimens after completion of TB treatment, unless contraindicated. Patients on EFV do not need lower lead in dosing when switching to NVP. Patients should be closely monitored for hypersensitivity and rash during the transition.

5.3 Patients coinfected with HBV

- HIV modifies the natural history of HBV infection, with higher rates of progression to advanced liver disease among persons with HIV/HBV co-infection. The presence of HIV is associated with greater rates of progression to cirrhosis and hepatocarcinoma which is correlated with the rate of HBV replication. The impact of HBV on HIV natural history is less known.

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

- NVP should be avoided in PLHIV and HBV with AST/ALT>5 x upper limit of normal

- 3TC and TDF are active against hepatitis B. Recent studies have demonstrated improved HBV response in patients with HBV associated cirrhosis to regimens that include both drugs.

- When AST/ALT > 3 x upper limit of normal with no evident potential causes like hepatotoxic drugs (fluconazol, NVP, anti-TB treatment…) one should consider to test for HBV co-infections when diagnostic test are available (HBsAg, anti-HBc, or anti-HBs). HBV DNA testing is now available at the Pasteur Institute. However, in most referral hospitals, only hepatitis B surface antigen testing is available, but this test is a strong indicator of chronic HBV infection.

- If HBV surface antigen is negative, patients do not have HBV or are immune to HBV and should received standard ART (see section 5).

There are two types of chronic HBV infections, chronic <u>inactive</u> HBV infection and chronic <u>active</u> HBV infection.

- Patients are considered to have chronic <u>inactive</u> HBV infection if:
  - HBV surface antigen is positive and AST/ALT <3 x ULN on two consecutive visits 3 months apart after 6 months of ART,
  - These patients should receive standard ART regimens at CD4 <350 cells/mm^3 that include only 3TC (see section 5).

- Patients are considered to have chronic <u>active</u> HBV infection if:
    - HBV surface antigen is positive and AST/ALT >3 x ULN on two consecutive visits 3 months apart after 6 months of ART
    - **These patients should switch ART regimens to 3TC +TDF +EFV**

If HBV surface antigen test is positive and AST/ALT are greater than 3 x ULN after 6 months of ART on two consecutive visits 3 months apart, patients have chronic <u>active</u> HBV

Patients with chronic inactive or active HBV should be recommended to avoid or limit alcohol consumption and be counseled with the risk of HBV transmission.

It is recommended to avoid to stop abruptly any ART working on HBV because of the risk of worsening liver function (hepatitis flare).

When a patient with HBV/HIV co-infection have exacerbation of hepatitis, providers should seek expert advice. Hepatitis with HBV/HIV coinfection could also be due to:

- Discontinuation of NRTI with anti-HBV activity (3TC or TDF),
- Immune reconstitution with ART (with or without 3TC or TDF)
- Hepatotoxicity of antiretroviral drugs or OI drugs (fluconazole, anti-TB treatment…), or
- Emergence of HBV NRTI resistance (especially 3TC)

5.4 Pregnant women

- Pregnant women should start ART if eligible (CD4 count<350 cells/mm^3) and continue ART after delivery.
- All women who are not eligible for ART (CD4 count>350 cells/mm^3)during pregnancy should receive ARV prophylaxis with triple drug therapy from 14 weeks gestation as outlined in the National PMTCT Guidelines, 2010 guidelines (see Annex 7 for summary of ARV prophylaxis for non-ART eligible pregnant women).

Recommended ART during pregnancy is **AZT+3TC+ NVP**. There is a small increased risk of NVP-induced hepatitis in pregnant women with CD4 counts 250-350 cells/mm3. These patients should be started on NVP with monitoring liver function test every two weeks during the first month and every four weeks during the 2^{nd}, 3^{rd}, and 4^{th} months of therapy.

EFV is an alternative to NVP but should not be initiated during first trimester due to the risk of neural tube defects. EFV is safe in 2nd and 3rd trimesters.

If providers have any questions regarding suitable ART for pregnant women, an expert should be consulted. Below are some alternatives for providers to use in consultation with an expert in special circumstances that may arise in pregnant women on ART:

- If AST/ALT are >5 times upper limit of normal:
    - First trimester - switch to AZT+3TC+TDF, then switch to AZT+3TC+EFV in second trimester
    - Second or third trimester – switch to AZT + 3TC + EFV

- If pregnant patients have any other contraindication to NVP (moderate to severe rash):
    - First trimester - switch to AZT+3TC+TDF, then switch to AZT+3TC+EFV in second trimester
    - Second or third trimester – switch to AZT + 3TC + EFV

- If pregnant patients have a contraindication to EFV and NVP regardless of trimester, patients should be switched to LPV/r based regimen.

- If pregnant patients have a contraindication to AZT and d4T, TDF is also an acceptable alternative. The safety of TDF on bone demineralization of the fetus is theoretical at this time and patient registries have not found a significant association.

- Women on ART who become pregnant should continue ART but adaptation to the duration of pregnancy should be made:

    - If pregnancy is recognized during the first eight weeks of pregnancy and the mother is already on EFV regimen, EFV should be changed to NVP
    - If pregnancy is recognized at 8-12 weeks and mother is on already on an EFV regimen, she should continue on her EFV based regimen.

- For women who have already received PMTCT during a previous pregnancy within the past twelve months:

    - It is acceptable to initiate ART with an NNRTIs-based regimen if a pregnant woman has previously received PMTCT in the form of

single dose NVP <u>with</u> an ARV "tail" or continuation of 3TC+AZT for at least seven days.

- **If she has received PMTCT in the form of single dose NVP <u>without</u> an ARV "tail" or continuation of 3TC+AZT for at least seven days, she should be started on a LPV/r based regimen due to a high risk of having PMTCT induced NNRTI resistance.**

- 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 Pediatric Guidelines for the use of Antiretroviral Therapy, 2011 and PMTCT Guidelines, 2010.

    - Women taking ARVs who decide to breastfeed should continue taking ARVs.

6. Continuing antiretroviral therapy

6.1 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 (<90%) 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 and community based care as part of the CoC framework.

- 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 by MoH 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, lipoatrophy or 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, and increased risk of non-HIV associated cancers.

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

6.2 Support behavior change and disclosure

- A good time to explore risk behavior is after a few months of ARV therapy. Provide positive prevention messages according to National Program SOPs asking about sexual behavior, condom use, STI checking, planned pregnancies and birth spacing methods. Support the development of safe sexual practices over time.

- Reinforce education to PLHIV that they 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 provide greater support to PLHIV, but this must be balanced against the risk of stigma and discrimination.

6.3 Monitoring ARV therapy

Anyone starting ART should see their doctor:

- 2 weeks after starting ART
- Monthly until they understand well their ART regimen and adherence, and are clinically and immunologically stable.
- Then at least every 3 months, to pick up medication and discuss adherence and any new symptoms.

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.

- TB symptom screening according to 3Is TB screening algorithm should be done at each visit (see 3Is SOPs) and follow suspected TB algorithm for case positive clinical findings

Determine whether symptoms are due to:

- New illness, including a new OI
- Drug side effects
- Symptoms of Immune reconstitution (See Section 6.7)
- Perform routine laboratory monitoring (See Table 9). Additional investigations should be performed as clinically indicated.

Table 9: Recommended routine laboratory monitoring during ART

Laboratory test	Essential	Optional
CD4 count	Every 6 months	If clinically indicated
AST / ALT	During first 2-4 months of NVP, INH, TB therapy, or during pregnancy with CD4 counts 250-350 cells/mm^3	If clinically indicated
Pregnancy test	Essential if using EFV	
CBC	M1 and every 3 months if using AZT	If clinically indicated
Chest X-ray	If required for TB assessment (see 3Is SOPs)	If clinically indicated
HIV viral load	After 24 months of ART, then every 12 months or to assess treatment failure (see section 8.3)	
Creatinine	Every 3-6 months if using TDF	If clinically indicated
Phosphate		Every 3-6 months if using TDF(to detect induced renal tubulopathy or Fanconi syndrome)
Amylase		If clinically indicated
Lipids		Every 12 months if on d4T,EFV, or PI
Hepatitis B Surface Ag and Antibody	if AST/ALT>3 or follow-up for previous positive HBV surface Ag test	If AST/ALT<3, or clinically indicated

6.4 Diagnose and manage opportunistic infections

Despite successful ARV therapy, OIs can still occur (see National Guidelines the use of Prevention and Treatmetn of Opportunistic Infections in in Adults and Adolescents, 2011). The development of an OI may indicate treatment failure (see Section 8) and warrant targeted immunological and eventually virological testing.

6.5 Diagnose and manage ARV side effects

- 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 10 for common side effects of ARVs and Table 20 for advice on the prevention and management of side effects.

Table 10: Common ARV side effects

Drug and drug class	Drug specific side effects				
	Skin	Blood	Gastrointestinal	Neuromuscular	Other
Zidovudine (ZDV or AZT)		Anemia 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	Lactic acidosis
Abacavir (ABC)					Hypersensitivity syndrome
Tenofovir (TFV or TDF)					No common side effects, occasional diarrhea, Tubulopathy (Fanconi syndrome)
Nevirapine (NVP)	Rash		Hepatitis		Hypersensitivity syndrome
Efavirenz (EFV)	Rash		Hepatitis	Frequent and diverse CNS effects*	Teratogenicity
Lopinavir + Ritonavir (LPV/r)			Diarrhea	Parasthesia	Hyperlipidemia

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

6.6 Changes ARV regimen because of side effects

There are times when ARVs have to be discontinued due to intolerance or adverse side effects. When discontinuing drugs, care should be taken not to expose the virus to subtherapeutic drug levels that could lead to resistance.

- If needing to temporarily cease or switch NVP or EFV alone, continue the other NRTIs for 7 days after NVP or EFV is ceased because the half-life of these NRTIS is longer than the half-life of NRTIs. This will limit the development of resistance to NNRTIs for possible future use.
- In some cases, however, all drugs should be stopped simultaneously when patients experience a grade 3 or 4 adverse event to ART.
- See Table 11 and Annex 2 for more details.

Table 11: What ARV to change to because of side effects

Drug	Side effect	Suggested immediate action	Suggested future action
NRTI	Lipoatrophy	Consider changing NRTI (d4T or ddI or AZT) to TDF	Can use these drugs again, but will make lipoatrophy worse
	Lactic acidosis	Stop all ARVs. Support patient and then change NRTI to TDF	Try to avoid using AZT, Never use d4T or ddI again
AZT	Anemia (Hb<8 g/dl or fall > 25%)	Change AZT to d4T or TDF	Avoid AZT
	Neutropenia (neutrophils < 750 cell/ml^3)	Change AZT to d4T or TDF	Avoid AZT
d4T	Peripheral neuropathy (moderate or severe)	Change d4T to AZT or TDF and give symptomatic treatment with amitriptyline and vitamin B6)	Avoid d4T
ddI	Lactic acidosis, pancreatitis, peripheral neuropathy, lipoatrophy	Stop all ARVs if lactic acidosis and moderate pancreatitis (amylasae>1.5x uln). Support patient until stable and then change ddI to another NRTI (not d4T) such as TDF. May immediately change ddi to another NRTI (not d4t) for other side effects (see Table 20 or figure 1)	Avoid ddI, consider switch to another NRTI such as TDF
	Pregnancy (teratogenicity)	Consider switch to TDF	May restart ddi after pregnancy
TDF	Renal toxicity (renal tubular dysfunction)	Change to AZT	Avoid TDF in future

ABC	Hypersensitivity Syndrome:	Change ABC to another drug depending on previous experience	Never use ABC again as reuse can be fatal
NVP	Rash – dry (no mucosal involvement or fever)	Continue NVP at current dose, treat with antihistamines	If rash resolves and patient on lower lead in dose for more than two weeks, attempt to increase to standard dosing, if rash reoccurs, switch to EFV
	Rash – moderate to severe (eg bullae, "wet"), no mucosal involvement, nonprogressing	Change NVP to EFV after resolution of cutaneous symptoms	Never use NVP again
	Rash – complicated (mucosal involvement or fever)	Stop all ARVs and cotrimoxazole, restart when stable. Change NVP to PI	Never use NVP or EFV
	Hepatitis	If AST/ALT>5 upper limit of normal discontinue ART until stable, then change NVP to EFV. Otherwise can change immediately to EFV.	Never use NVP again
	Hepatitis – severe or life threatening	Change NVP to PI	Never use NVP or EFV again
EFV	CNS effects – severe	Change EFV to NVP	Avoid EFV
	Pregnancy (teratogenicity)	Change EFV to NVP if within first 8 weeks of pregnancy	Can use EFV again when not pregnant
	Rash – dry (no mucosal involvement or fever)	Treat with antihistamines. EFV rash often stops spontaneously after 3−5 days without need to change ARV. If no improvement, switch to NVP	Never use EFV again, if intolerant to NVP then use boosted PI
	Rash – moderate to severe (eg bullae, "wet"), no mucosal involvement, nonprogressing	Change EFV to NVP	Never use EFV again, if intolerant to NVP then use boosted PI
	Rash – complicated (mucosal involvement or fever)	Change EFV to boosted PI	Never use NVP or EFV
LPV	Metabolic complications (hyperglycemia, hyperlipidemia) – uncontrolled	Change PI to non-PI if unable to be controlled	Avoid using PI again if possible

6.7 Diagnose and manage 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 ART 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.
- Reaction to remnants or antigens of previous OIs after treatment

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 2-8 weeks after commencing ARV, but can occur any time in the first 6 months of ART, and in rare cases, later. The risk of IRIS is highest when ART is started early in patients with very low baseline CD4 counts. However, symptoms are rarely life threatening, and the risk of death from IRIS is much lower than the risk of death from other OI that can occur if ART is delayed.

TB is the most common cause of immune reconstitution syndrome. This is similar to 'paradoxical reactions' seen in non-HIV infected people being treated for TB. The most common symptoms include fever and an increase in the size or number of 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 IRIS from 1) drug toxicity or 2) TB treatment failure due to drug resistance or poor adherence. This can be difficult.

The usual approach to diagnosis and management is to:

- Continue ART
- Aggressively investigate for new OI or active OI that is failing treatment. This usually requires checking blood cultures, new chest x-ray, and lumbar puncture if CNS symptoms are present. Any new or worsening lymph node lesions or skin lesions are important clues and should be biopsied if results of blood and CSF do not reveal the diagnosis. Patients with worsening TB symptoms should have sputum or lymph node aspiration culture and sensitivity testing to evaluate for multi-drug resistant TB or MAC.

- Start/continue treatment for the symptomatic infection when discovered
- Non-steroidal anti-inflammatory agents can be used to reduce symptoms related to inflammation, e.g. lymphadenitis and fever.
- If necessary, a short course of corticosteroids are occasionally required if symptoms become severe (e.g. dyspnea, CNS symptoms, renal obstruction).

7. Minimize the development of resistance

- HIV resistance to ART reduces the efficacy of ARV therapy and increases the cost of the ARV regimen. Furthermore, ARV-resistant strains of HIV can be transmitted to others (through normal modes of transmission).

- HIV can rapidly develop resistance to ART when not taken correctly. Good Suppporting adherence every time can prevent the development of resistance. Imperfect adherence is the most important cause of drug-resistant HIV (See Section 8)

- 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.

- MoH does not permit to use 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 7 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 as well.

8. How to recognize treatment failure?

Treatment failure and the decision to switch to an alternative ARV regimen cannot be based on one laboratory result alone. After identifying clinical, immunological, and/or virological failure (see sections below), the provider can focus the decision to switch therapy based the likelihood of viral resistance once the causes listed below are excluded.

Some common causes for treatment failure not related to viral resistance are:

- Inadequate adherence:
  - Missing doses
  - Not appropriate time
  - Not appropriate dose
- Inadequate drug levels:
  - Under-dosing
  - Poor absorption (diarrhea)
  - Varying pharmacokinetics
  - Metabolic changes
  - Drug-Drug interactions

It should not be concluded that an ARV regimen is failing until:

- The individual has been on the current regimen for at least 6 months
- Adherence to therapy has been assessed and considered to be optimal (>90%)
- Any opportunistic infections have been treated, and
- Immune reconstitution inflammatory syndrome (IRIS) excluded.

Table 12 can aid providers in stepwise approach for "ruling-out" causes of treatment failure other than viral resistance.

Table 12: Identifying and addressing causes of treatment failure

Steps	Action
Step 1	• Asses clinical, immunological, and virological failure to decide if treatment failure is likely
Step 2	If any of the above is present: • Confirm clinical or immunological failure with viral load whenever possible • 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 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 • Change drugs/doses to avoid under-dosing or drug interactions.
Step 4	• Decide whether ART regimen should be changed (What second-line regimen to start)

8.1 Clinical Failure

- Clinical failure in adults on ART is defined by the development of any new or recurrent stage 3 or 4 events, except pulmonary TB, at least 6 months after starting new ART regimen.

  - These events may include:
    - Occurrence of new opportunistic infections or malignancies, or recurrence of infections, such as oral candidiasis that is refractory to treatment, or esophageal candidiasis

- Unexplained anemia (below 8 g/dl), neutropenia (0.5 x 10^9/l), and/or chronic thrombocytopenia (50 x 10^9/l)
- Wasting of more than 10% of body weight after not responding to nutrition therapy
- Chronic diarrhea for greater than one month

- If patients develop new HIV related illness prior to six months of ART initiation, these symptoms are unlikely related to failure of ART. Rather, these illnesses could reflect difficulty with adherence, side effects of ARV therapy, acute OI in the setting of continued immune deficiency, or IRIS during immune recovery. Providers should manage symptoms and continue with ART.
- Pulmonary TB can occur at any level of immune function. If a patient develops Pulmonary TB on ARV therapy, providers should treat accordingly. If patients do not respond to initial TB treatment and patient has been on ART for at least six months, providers should check CD4 count for immunological failure and check a viral.
- When clinical failure is detected or suspected, immunological and virological failure and should be assessed (see sections 8.2 and 8.3)
- Results of CD4 and HIV viral load testing will either confirm or rule-out treatment failure should be used to make the final decision regarding moving to 2nd line treatment. Table 13 highlights the management of patients who present with clinical failure.

Table 13: Management of Clinical Failure after Stage III or IV event

Clinical event after ≥6 months on ART	Evaluation, assessment of immunological Failure, and initial management	Follow-up management at 1-2 weeks
Stage 3 event (except pulmonary TB)	• May be due to: - persisting immune deficiency - Treatment failure - IRIS, but less common after 6 mo • Treat event as appropriate • Assess adherence and intensify counseling • Assess nutritional status and access to food • Check CD4 and/or viral load • Follow-up within 2 weeks to monitor for response	• Recheck CD4 if viral load not obtained • Switch to 2nd line if CD4 reveals immunologic failure if unable to obtain • If CD4 above threshold for immunological failure, wait and obtain viral load • Switch to 2nd line if viral load>5000 copies/ml
Stage 4 event	• Treat event as appropriate • Assess adherence and intensify counseling • Assess nutritional status and access to food • Follow-up closely or hospitalize as necessary • Check CD4 and/or viral load • Begin planning for possible ART regimen switch • Follow-up within 1-2 weeks to monitor for response	• Recheck CD4 if viral load not obtained • Switch to 2nd line if CD4 reveals immunologic failure if unable to obtain • If CD4 above threshold for immunological failure, wait and obtain viral load • Switch to 2nd line if viral load>5000 copies/ml • If viral load is lower than detectable limit, do not switch to 2nd line

8.2 Immunological Failure

Immunological failure can be assessed after six months of ART and is defined as:

- A decrease in CD4 cell count to pre-therapy baseline level or below after 6 months of ART, without OI to explain transient CD4 cell decrease, or
- 50% fall from on-therapy CD4 peak level, without infection to explain transient CD4 cell decrease after 6 months of ART, or
- Persistence CD4 level below 100 cells/mm^3 after 12 months of therapy

Indications of possible treatment failure as described above may require switching ARV regimen. However, CD4 count is most helpful in "ruling-out" and <u>not</u> "ruling-in" treatment failure due to transient decreases of CD4 count during intercurrent illnesses. For this reason, providers should confirm immunological failure with a repeat CD4 test after two weeks. In order to confidently and quickly "rule-in" or diagnose treatment failure due to viral resistance, providers should access viral load testing whenever

possible. If viral load testing is not available, this is an important and complicated decision point in the setting of an asymptomatic patient with isolated immunological failure (immunological failure without clinical failure) which should be discussed with an expert.

ANY DIAGNOSIS OF ISOLATED IMMUNOLOGICAL FAILURE SHOULD BE CONFIRMED WITH A REPEAT CD4 COUNT AFTER 2 WEEKS AND DISCUSSED WITH AN EXPERT OR OBTAIN VIRAL LOAD IMMEDIATELY

See Table 14 for assessing and managing isolated immunological failure.

Table 14: Management of isolated immunological failure

Scenario	Duration of ART	Diagnosis	Action
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	• Reheck CD4 count after 2 weeks, 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	• Reheck CD4 count after 2 weeks, especially if first CD4 count was performed during an intercurrent illness. • If CD4 count is confirmed then check HIV viral load if available
Persistent CD4 count less than 100 cells/mm^3	> 12 months	• May be due to: o 'Normal' response, especially in older people o Treatment failure o Laboratory error	• Reheck CD4 count after 2 weeks, especially if first CD4 count was performed during an intercurrent illness. • If CD4 count is confirmed then

			check HIV viral load if available

8.3 Virological Failure

Assessing virological failure is an essential component of determining treatment failure. Virological failure improves the accuracy of diagnosing treatment failure and can avoid unnecessary switches in ART when current regimens are effective. Similarly, virological failure can lead to interventions such as adherence counseling and elimination of drug-drug interactions to resuppress the virus without changing to second-line therapy.

Virological failure is defined as detectable viral load of >5000 copies of viral RNA/ml.

Targeted testing based on clinical and immunological failure will be initiated this year and limited routine monitoring of viral loads will be initiated once viral load testing capacity is increased **NCHADS will send out announcement once viral load capacity is high enough to start ROUTINE viral load testing- eligibility criteria #6)**. As testing is rolled out, this program will be closely monitored and the present guidelines will be regularly reviewed in light of program results and viral load testing technological advances. Table 15 summarizes current VL testing eligibility.

Table 15: Viral load testing eligibility criteria

Send viral load testing if any of the following occurs:
1) Clinical failure in adults on ART is defined by the development of any new or recurrent stage 3 or 4 events, except pulmonary TB, at least 6 months after starting new ART regimen, or 2) A decrease in CD4 cell count to pre-therapy baseline level or below after 6 months of ART, without OI to explain transient CD4 cell decrease 3) 50% fall from on-therapy CD4 peak level, without infection to explain transient CD4 cell decrease after 6 months of ART, or 4) Persistence CD4 level below 100 cells/mm^3 after 12 months of therapy, or 5) Repeat testing after previously detectable viral load, or 6) As annual routine monitoring beginning after at least 24 months of ART therapy

NCHADS will send out announcement once viral load capacity is high enough to start LIMITED ROUTINE viral load testing (eligibility criteria #6)

8.4 When to Switch to Second-Line Therapy?

It is important to remember that virological failure proceeds immunological failure which proceeds clinical failure. Patients suspected of treatment failure who are found to have an undetectable viral load should NOT be switched to 2nd line therapy.

Providers should not switch to 2nd line regimens based on clinical failure alone unless in a severely ill patient with a new stage 4 condition under the guidance of expert advice. Likewise, patients with isolated immunological failure should not switch to a 2nd line regimen without seeking expert advice. Some experts consider certain Stage II conditions such as PPE as an early sign of treatment failure and will recommend a switch to 2nd line therapy.

Thus, there are three common scenarios a provider may encounter that should lead to a switch to second line therapy.

1) A patient <u>with</u> clinical and immunological failure without access to viral load testing
2) A patient <u>with</u> clinical and/or immunological failure who has a detectable viral load greater than 5000 copies/ml; or
3) A patient <u>without</u> clinical or immunological failure who has a detectable viral load greater than 5000 copies/ml on repeated routine monitoring tests

Scenario 1 - In the setting of an acute stage 3 or 4 clinical event, providers will have to make a decision whether to switch to second-line in the context of the patients clinical condition and immune status.

Scenario 2 – If patients with clinical and immunological failure have a detectable viral load > 5000 copies/ml, providers should switch to second-line therapy.

Scenario 3 - For those patients without clinical or immunological failure who are eligible for routine viral load monitoring after 24 months of ART, providers should seek follow up viral load testing at 2 months following adherence boosting before switching to second line therapy.

However, if at any time, a patient develops clinical or immunological failure during the follow-up period for a routine viral load test, providers may consider an immediate switch to second line once a repeat viral load is detectable under consultation with an expert. This point cannot be emphasized more. **Repeated clinical follow-up on and adherence monitoring on a monthly basis is essential to monitoring a patient with isolated virological failure.** In cases, where virological failure is due

to viral resistance, patient's clinical status may decline rapidly before the next scheduled viral load measurement.

Table 16 summarizes steps a provider can follow during routine testing. In addition, annex 4 provides the same information in an algorithm form to guide clinicians in deciding what actions to take based on routine monitoring viral load results.

Table 16: Management of suspected virological failure based on routine monitoring in asymptomatic patients

Plasma viral load (VL)	Recommendation
Undetectable	• Repeat VL in 12 months
<1,000 copies/mL (1.7 - 3.0 log)	• Repeat VL in 6 months[1] • Assess adherence, increase counseling as needed
>1,000 – 5,000 copies/mL (3.0 – 3.7 log)	• Repeat VL in 2 months • Intensify adherence counseling • Investigate for drug-drug interactions or inadequate dosing • Consider 2nd line therapy if repeat VL remains between 1,000 and 5,000 copies/mL *and* evidence of clinical or immunological failure *and* adherence is >90% with expert consultation, otherwise recheck VL in 3 months • Switch to 2nd line therapy if repeat VL is >5,000 copies/mL
>5,000 copies/mL (>3.7 log)	• Repeat VL in 2 months • Intensify adherence counseling • Investigate for drug-drug interactions or inadequate dosing • Then switch to 2nd line therapy if repeat VL is >5,000 copies/mL and adherence is >90%

[1]If 3 successive VL measurements remain between 50 and 1,000 copies/mL without evidence of immunologic or clinical failure, decisions regarding 2nd line must be made on an individual basis. Discuss with an expert.

9. What Second-Line Regimen to Start?

The preferred second-line regimen is based on the individual's failed first-line regimen. In the absence of viral genotype and phenotype testing, the suggested second-line regimens attempt to limit common overlapping resistance profiles with ARVs used in the patients' first-line regimen. Although there are millions of possible mutations, there are some major mutations that drive decisions on second-line therapy, including:

- K103N, Y181 I/C/V, and V106 A/M mutations to NNRTIs
- Thymidine analogue-associated mutations to d4T and AZT, and
- K65R mutation to TDF, ABC, and ddi (also d4T in Cambodia)

NNRTI resistance is most common in failed first-line regimens. As a result, all second line therapy relies on PI based boosted regimens (LPV/RTV or ATV/RTV***).

TDF + 3TC continues to be the preferred second line NRTIs in Cambodia. Patients are eligible for TDF if they have no prior renal disease and their glomerular filtration rate (GFR)is greater than 30. TDF needs to be dosed for baseline renal function (300 mg daily if GFR>50 ml/min and 300 mg every other day if GFR between 30 and 49 ml/min. If patients do not qualify for TDF based on renal function, ABC is the suggested alternative.

The following table summarizes recommended second-line regimens based on failed first-line regimens:

Table 17: Standard Second-line ART regimen*

Recommended Regimen	TDF+3TC+LPV/RTV**
Alternative Regimen	ABC+3TC + LPV/RTV***

*For patients on rifampicin TB treatment, increase PI dosing to LPV 400mg/RTV 400 mg twice daily by administering an additional three RTV 100 mg tablets with each dose. If individual RTV 100 mg tablets are not available, double the standard LPV/RTV dose to LPV 800mg/RTV 200 mg twice daily. Increased dosing should continue until two weeks after completion of the TB treatment with rifampicin.

** Cockcroft-Gault formula. GFR = (140-age) x (wt. in kg) x(0.85 if female)/(72 x creatinine in mg/dl). TDF dosing for GFR>50 ml/min is 300 mg once daily and for GFR 30-49 ml/min is 300 mg every 48 hours. If GFR<30 use alternative regimen.

***__Atazanavir/Ritonavir (ATV/r)__ is a preferred PI that may be used in place of LPV/r as part of a recommended second line regimen. ATV/r is well-tolerated and has comparable efficacy to LPV/r. Single ATV (300mg), heat-stable RTV (100mg) and the fixed dose combination of ATV/r (300mg/100mg) will be available in Cambodia in 2012.

10. What to do when second-line ART fails?

Cambodia currently does not have third-line regimens. NCHADS will continue to monitor the level of resistance among PLHIV to second-line.

Until then, it is best practice to continue the failing second-line regimen. **All providers should seek expert advice when second-line regimens fail as there may be alternatives regimens consisting of available ARVs that may better suppress the virus.**

11. ART in special situations

11.1 Adults with previous exposure to ARVs

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 combination. Use the original combination if this was appropriate, well tolerated and taken correctly.

If the patient has been of ART that included an NNRTI greater than two weeks prior to reinitiation, providers should use lead in dosing when starting a NVP based regimen (see Table 8).

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 is a second-line PI based regimen that includes a different NRTI.

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 with close monitoring for treatment failure.

11.2 Women with HIV of child bearing age

Birth spacing (BS) services are an essential component of the package of prevention and care activities for PMTCT. Preventing unwanted pregnancies among HIV-infected women can reduce maternal and infant mortality and, particularly amongst high-risk women, reduce the number of new HIV infections occurring through vertical transmission. Condoms, used consistently and correctly, can prevent both pregnancy and infectious diseases, including Hepatitis B, STIs and HIV. Dual protection, the use of condoms with another modern contraceptive method to prevent both infection and pregnancy, should be promoted.

HIV-infected women who do not wish to become pregnant should be referred to BS services and counseled on the risks and benefits of available modern contraceptive methods and be helped to make an informed choice. In addition to condoms, other birth spacing methods such as oral contraceptive pills and injectable progestogen will also be made available at OI/ART clinics, to enable women already known to be HIV-infected to access contraceptive services more easily.

HIV-infected women with unintended pregnancies should be offered reliable information and compassionate counseling, including information on where and when a pregnancy may be legally and safely terminated, and should be referred to Referral Hospitals or other certified centers providing comprehensive, safe abortion care (please see National Guidelines for the PMTCT of HIV, 2010).

When HIV-infected women use oral contraceptives, patients and providers should know that NVP and most PIs lower blood levels of oral contraceptive pills (OCP), so additional or alternative methods of contraception should be used (i.e. 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 (i.e. condoms) should be used in these situations as well.

Women living with HIV should also recognize the increased importance of routine gynecological screening. The rates of genital warts, cervical dysplasia, and invasive cervical carcinoma are significantly increased in women with HIV.

11.3 Adolescents

These guidelines can be applied to adolescents greater than 14 years of age who are close to sexual maturity (Tanner stage IV or V). For information on ARV therapy on children, younger adolescents, or less sexually mature adolescents (Tanner stage I, II, or III) please refer to updated National Guidelines on the use of Pediatric Antiretroviral Therapy, 2011.

During adolescence healthy children undergo physical, psychological and sexual

growth and maturation characteristic of puberty. Many perinatally HIV-infected children in Cambodia have entered into the adolescent age group. It should also be acknowledged that some adolescents will acquire HIV infection as teenagers through adult behaviors, including sexual contact and intravenous drug use. The perinatally infected adolescent who is identified at a young age will generally have a different clinical course and HIV treatment history than the adolescent who acquires infection as a teenager.

Unique considerations must be taken into account when using the NNRTI class of drugs in **adolescent girls**:

- Because EFV may be toxic to the growing fetus, it should not be used in adolescent girls who are at risk for pregnancy (i.e. sexually active and not using adequate contraception), or who are in the first trimester of pregnancy.
- Symptomatic NVP-associated hepatotoxicity or serious skin rash, while uncommon, are more likely to be seen in adolescent females with higher CD4 counts (> 250 cells/mm) who have never received ARV treatment. NVP should therefore be used as first-line but with caution in adolescent girls with absolute CD4 counts between 250 and 350 cells/mm^3.

Adherence to long-term therapy is particularly difficult among adolescents. Reasons for this may include an unstructured lifestyle, lack of social supports, not knowing their HIV status, being in denial of their HIV status, and stigma. Simple ARV regimens will maximize adherence. Additionally, disclosure to the adolescent of his/her HIV status, while difficult, often helps the adolescent to adhere better to ARV medications. For these reasons, it is especially important that young people:

1) are informed about their HIV status;
2) are well educated about their condition, its treatment and the importance of adhering to care and ART;
3) are confident in their ability to talk about HIV with those whom they want to know about their condition; and
4) have a strong support system so that they know where to obtain help and advice when necessary

Positive prevention counseling provides the adolescents with the knowledge and skills to protect themselves and their sexual partner(s) from STI and HIV infection or re- infection. Pediatric counselors or pediatricians must provide positive prevention counseling to HIV infected adolescents at every visit, or more frequently as needed. The content of counseling will vary according to individual needs. In general, counselors should talk with adolescents about:

- Route of HIV transmission
- Delay of sexual activity;
- Safety/risk of different sexual practices;
- Communication and negotiation skills for safer sex including condom use;

- Issue of partner disclosure; and
- HIV and unintended pregnancies.

11.4 Post-exposure Prophylaxis

Providing a safe working environment for healthcare personnel (HCP) is both a basic worker's right and essential to the functioning of an effective health care system. To reduce the risk of exposure to communicable diseases, it is essential that universal precautions, as described in the November, 2002 Guideline (1) be practiced at every medical institution. Even when universal precautions are practiced, accidental needle sticks and other accidental exposures do occur. HCP working with HIV infected patients, who experience such accidental exposures, are at risk of being infected with HIV. Post-exposure administration of antiretroviral drugs has been shown to reduce the risk of becoming infected. **The National Guidelines for Management of Occupational Exposure of Health Care Workers To HIV/AIDS (2006) should be referred to in the case of an event.**

In general, the risk of HIV transmission after occupational exposure is approximately 0.3% after percutaneous exposure (2), 0.09% after exposure to mucous membranes (3), and less than 0.09% for exposure to non-intact skin (4). Exposure to the following bodily fluids are thought to carry some risk of transmission though that risk is likely much lower than that associated with exposure to blood: cerebrospinal fluid, synovial fluid, pleural fluid, peritoneal fluid, pericardial fluid, and amniotic fluid. Contact with semen and vaginal secretions, while cause of sexual transmission, has not been implicated in occupational transmission from patients to providers. Contact with the following bodily fluids confer no recognized risk to the exposed health care worker unless they contain gross blood: feces, nasal secretions, saliva, sputum, sweat, urine, and vomitus.

"Exposure" is defined as a percutaneous injury or contact of mucous membrane or non-intact skin with blood, tissue, or other potentially infectious body fluids. In addition to the summary step 1-2-3 below, a flow chart of the necessary steps after an exposure in included as annex 3.

Step 1: Wound Management, Initial Counseling and Evaluation

Upon notification by a healthcare professional of work related exposure to potentially infected bodily fluids of a patient, the exposure site should be washed with soap and water for three minutes; mucous membranes should be flushed with water for ten minutes. Tap water is adequate for irrigation. There is no need to delay washing in order to secure sterile water or saline solution.

If the source patient's HIV status is unknown, s/he should be counseled to undergo a rapid HIV test, which should be done as quickly as the source patient will allow. The counseling should take place in a confidential setting and the source patient's legal right to refuse testing respected. If the source patient does refuse testing on site, or if the source patient cannot be identified, the known risk factors of the source patient or the community in which the exposure occurred should be used to assess likelihood that exposure was to an HIV infected patient. If the source patient prefers to be tested for HIV at an established VCCT site, the decision to treat the exposed provider should not be delayed. **Treatment should be started within FOUR hours of exposure whenever possible and not be delayed more than 72 hours**.

Treatment can be stopped if after initiating treatment, the source patient proves to be HIV negative. If the source patient is known to be HIV positive, stage of infection should be noted and past or present use of antiretroviral therapy should be specifically identified. If the source patient is highly treatment experienced and therefore at risk of having drug resistant virus, expert advice should be sought regarding alternate drug regimens for PEP. However, treatment should not be delayed; if consultation is not immediately available, standard treatment should be started and switched if consultant so advises.

Evaluation of the exposed health care professional should also take place in a confidential setting. Work-up consists of an HIV test. If the exposed HCP prefers that this be done at a VCCT site, that preference should be respected and treatment, if otherwise indicated, should not be delayed. If the HCP proves to be HIV+ at baseline, PEP should be stopped and the HCP referred for treatment of HIV.

The nature of the exposure must also be assessed. The HCP with exposures detailed in the algorithm should be offered PEP. Providers with less significant exposures should be reassured that their exposures are trivial and require no treatment.

Step 2: Treatment and Monitoring

Once the decision to treat has been made, treatment should be initiated as quickly as possible, and delays caused by filling out paperwork avoided. The paperwork can be completed after a first dose is given. The treatment regimen is provided by the National Center for HIV/AIDS, Dermatology, and STIs and includes **Zidovudine 300mg plus Lamivudine 150mg in a combination tablet every 12 hrs for 28 days**.

It is recommended that a four day supply be dispensed initially with a return appointment scheduled for three to four days later, at which time HIV status of both the source patient and HCP can be reviewed if not already known, side effects and adherence issues discussed. If an alternative regimen is warranted based on poor

tolerance of Zidovudine, Stavudine 30 mg should be substituted for Zidovudine and taken in a combination tablet with Lamivudine 150 mg twice daily to complete the 28 day course. An additional visit 10 to 12 days later to discuss difficulties with regimen and to assure good adherence is also recommended. In cases of known exposure to a potentially resistant virus, a three-drug regimen can be prescribed. Typically, a three-drug regimen for post exposure includes a protease inhibitor such as LPV/r should be added to the dual nucleoside combination.

Follow-up HIV testing should be done at 3 months and 6 months post exposure and counseling given regarding abstaining from donating blood and appropriately protecting sexual partners until HIV is ruled out at 6 months.

Step 3: Reporting

A report must be completed at the medical center where PEP is provided for every provider who presents with an exposure. This should include all reported exposures including those judged to be clinically insignificant and not warranting treatment. A copy of the report should be kept in the health care institution and a copy sent to a central reporting office at NCHADS.

Annexes

Annex 1: WHO Tables

WHO staging system adults and adolescents

Clinical stage 1
Asymptomatic Persistent generalized lymphadenopathy
Clinical stage 2
Moderate unexplained weight loss (under 10% of presumed or measured body weight) Recurrent respiratory tract infections (sinusitis, tonsillitis, otitis media, pharyngitis) Herpes zoster Angular cheilitis Recurrent oral ulcerations Papular pruritic eruptions
Clinical stage 3
Unexplained severe weight loss (over 10% of presumed or measured body weight) Unexplained chronic diarrhoea for longer than 1 month Unexplained persistent fever (intermittent or constant for longer than 1 month) Persistent oral candidiasis Oral hairy leukoplakia Pulmonary tuberculosis Severe bacterial infections (e.g. pneumonia, empyema, meningitis, pyomyositis, bone or joint infection, bacteraemia, severe pelvic inflammatory

Clinical stage 4

HIV wasting syndrome *Pneumocystis*

jiroveci pneumonia Recurrent severe

bacterial pneumonia

Chronic herpes simplex infection (orolabial, genital or anorectal of more than 1 month's duration or visceral at any site)

Oesophageal candidiasis (or candidiasis of trachea, bronchi or lungs)

Extrapulmonary tuberculosis

Kaposi sarcoma

Cytomegalovirus disease (retinitis or infection of other organs, excluding liver, spleen and lymph nodes)

Central nervous system toxoplasmosis

HIV encephalopathy

Extrapulmonary cryptococcosis including meningitis

Disseminated nontuberculous mycobacteria

infection Progressive multifocal leukoencephalopathy

Chronic cryptosporidiosis

Chronic isosporiasis

Disseminated mycosis (histoplasmosis, coccidiomycosis)

Recurrent septicaemia (including nontyphoidal *Salmonella*)

Lymphoma (cerebral or B cell non-Hodgkin)

Invasive cervical carcinoma

Atypical disseminated leishmaniasis

Symptomatic HIV-associated nephropathy or HIV-associated cardiomyopathy

Source: Revised WHO clinical staging and immunological classification of HIV and case definition of HIV for surveillance. 2006.

WHO Diagnostic Criteria for HIV-related Clinical Events

Clinical event	Clinical diagnosis	Definitive diagnosis
Clinical stage 1		
Asymptomatic	No HIV-related symptoms reported and no signs on examination	Not applicable
Persistent generalized lymphadenopathy	Painless enlarged lymph nodes >1 cm, in two or more noncontiguous sites (excluding inguinal), in absence of known cause and persisting for 3 months or longer	Histology
Clinical stage 2		
Moderate unexplained weight loss (under 10% of body weight)	Reported unexplained weight loss. In pregnancy, failure to gain weight	Documented weight loss (under 10% of body weight)
Recurrent bacterial upper respiratory tract infections (current event plus one or more in last 6 months)	Symptoms complex, e.g. unilateral face pain with nasal discharge (sinusitis), painful inflamed eardrum (otitis media), or tonsillopharyngitis without features of viral infection (e.g. coryza, cough)	Laborator y studies if available, e.g. culture of suitable body fluid
Herpes zoster	Painful vesicular rash in dermatomal distribution of a ner ve supply does not cross midline	Clinical diagnosis
Angular cheilitis	Splits or cracks at the angle of the mouth not attributable to iron or vitamin deficiency, and usually responding to antifungal treatment	Clinical diagnosis
Recurrent oral ulcerations (two or more episodes in last 6 months)	Aphthous ulceration, typically painful with a halo of inflammation and a yellow-grey pseudomembrane	Clinical diagnosis

Clinical event	Clinical diagnosis	Definitive diagnosis
Papular pruritic eruption	Papular pruritic lesions, often with marked postinflammatory pigmentation	Clinical diagnosis
Seborrhoeic dermatitis	Itchy scaly skin condition, particularly affecting hairy areas (scalp, axilla, upper trunk and groin)	Clinical diagnosis
Fungal nail infections	Paronychia (painful red and swollen nail bed) or onycholysis (separation of nail from nail bed) of the fingernails (white discolouration, especially involving proximal part of nail plate, with thickening and separation of nail from nail bed)	Fungal culture of nail / nail plate material
Clinical stage 3		
Severe unexplained weight loss (more than 10% of body weight)	Reported unexplained weight loss (over 10% of body weight) and visible thinning of face, waist and extremities with obvious wasting or body mass index below 18.5. In pregnancy, weight loss may be masked.	Documented loss of more than 10% of body weight
Unexplained chronic diarrhoea for longer than 1 month	Chronic diarrhoea (loose or watery stools three or more times daily) reported for longer than 1 month	Not required but confirmed if three or more stools observed and documented as unformed, and two or more stool tests reveal no pathogens
Unexplained persistent fever (intermittent or constant and lasting for longer than 1 month)	Reports of fever or night sweats for more than 1 month, either intermittent or constant with reported lack of response to antibiotics or antimalarials, without other obvious foci of disease reported or found on examination. Malaria must be excluded in malarious areas.	Documented fever exceeding 37.6 °C with negative blood culture, negative Ziehl-Nielsen stain, negative malaria slide, normal or unchanged chest X-ray and no other obvious focus of infection

Clinical event	Clinical diagnosis	Definitive diagnosis
Oral candidiasis	Persistent or recurring creamy white curd-like plaques which can be scraped off (pseudomembranous), or red patches on tongue, palate or lining of mouth, usually painful or tender (erythematous form)	Clinical diagnosis
Oral hairy leukoplakia	Fine white small linear or corrugated lesions on lateral borders of the tongue, which do not scrape off	Clinical diagnosis
Pulmonary TB	Chronic symptoms (lasting at least 2 to 3 weeks): cough, haemoptysis, shortness of breath, chest pain, weight loss, fever, night sweats, plus EITHER positive sputum smear OR negative sputum smear AND compatible chest radiograph (including but not restricted to upper lobe infiltrates, cavitation, pulmonary fibrosis and shrinkage). No evidence of extrapulmonary disease.	Isolation of *M. tuberculosis* on sputum culture or histology of lung biopsy (together with compatible symptoms)
Severe bacterial infection (e.g. pneumonia, meningitis, empyema, pyomyositis, bone or joint infection, bacteraemia, severe pelvic inflammatory disease)	Fever accompanied by specific symptoms or signs that localize infection, and response to appropriate antibiotic	Isolation of bacteria from appropriate clinical specimens (usually sterile sites)
Acute necrotizing ulcerative stomatitis, gingivitis or periodontitis	Severe pain, ulcerated gingival papillae, loosening of teeth, spontaneous bleeding, bad odour, rapid loss of bone and/or soft tissue	Clinical diagnosis

Clinical event	Clinical diagnosis	Definitive diagnosis
Unexplained anaemia (below 8g/dl), neutropenia (below 0.5 x 10^9/l) and/or chronic (more than 1 month) thrombocytopenia (under 50 x 10^9/l)	No presumptive clinical diagnosis	Diagnosed on laboratory testing and not explained by other non-HIV conditions. Not responding to standard therapy with haematinics, antimalarials or anthelmintics as outlined in relevant national treatment guidelines, WHO IMCI guidelines or other relevant guidelines.
Clinical stage 4		
HIV wasting syndrome	Reported unexplained weight loss (over 10% of body weight) with obvious wasting or body mass index below 18.5, plus EITHER unexplained chronic diarrhoea (loose or watery stools three or more times daily) reported for longer than 1 month OR reports of fever or night sweats for more than 1 month without other cause and lack of response to antibiotics or antimalarials. Malaria must be excluded in malarious areas.	Documented weight loss (over 10% of body weight) plus two or more unformed stools negative for pathogens OR documented temperature exceeding 37.6 °C with no other cause of disease, negative blood culture, negative malaria slide and normal or unchanged CXR
Pneumocystis pneumonia	Dyspnoea on exertion or nonproductive cough of recent onset (within the past 3 months), tachypnoea and fever; AND CXR evidence of diffuse bilateral interstitial infiltrates, AND no evidence of bacterial pneumonia. Bilateral crepitations on auscultation with or without reduced air entry.	Cytology or immunofluorescent microscopy of induced sputum or bronchoalveolar lavage (BAL), or histology of lung tissue

Clinical event	Clinical diagnosis	Definitive diagnosis
Recurrent bacterial pneumonia (this episode plus one or more episodes in last 6 months)	Current episode plus one or more episodes in last 6 months. Acute onset (under 2 weeks) of symptoms (e.g. fever, cough, dyspnoea, and chest pain) PLUS new consolidation on clinical examination or CXR. Response to antibiotics.	Positive culture or antigen test of a compatible organism
Chronic herpes simplex virus (HSV) infection (orolabial, genital or anorectal) of more than 1 month, or visceral at any site or any duration	Painful, progressive anogenital or orolabial ulceration; lesions caused by recurrent HSV infection and reported for more than one month. History of previous episodes. Visceral HSV requires definitive diagnosis.	Positive culture or DNA (by PCR) of HSV or compatible cytology/histology
Oesophageal candidiasis	Recent onset of retrosternal pain or difficulty in swallowing (food and fluids) together with oral candidiasis	Macroscopic appearance at endoscopy or bronchoscopy, or by microscopy/histology
Extrapulmonary TB	Systemic illness (e.g. fever, night sweats, weakness and weight loss). Other evidence for extrapulmonary or disseminated TB varies by site: pleural, pericardial, peritoneal involvement, meningitis, mediastinal or abdominal lymphadenopathy, osteitis. Miliary TB: diffuse uniformly distributed small miliary shadows or micronodules on CXR. Discrete cervical lymph node *M. tuberculosis* infection is usually considered a less severe form of extrapulmonary tuberculosis.	*M. tuberculosis* isolation or compatible histology from appropriate site, together with compatible symptoms/ signs (if culture/histology is from respiratory specimen there must be other evidence of extrapulmonary disease)

Clinical event	Clinical diagnosis	Definitive diagnosis
Kaposi sarcoma	Typical appearance in skin or oropharynx of persistent, initially flat patches with a pink or blood-bruise colour, skin lesions that usually develop into violaceous plaques or nodules	Macroscopic appearance at endoscopy or bronchoscopy, or by histology
Cytomegalovirus disease (retinitis or infection of other organs, excluding liver, spleen and lymph nodes)	Retinitis only: may be diagnosed by experienced clinicians. Typical eye lesions on fundoscopic examination: discrete patches of retinal whitening with distinct borders, spreading centrifugally, often following blood vessels, associated with retinal vasculitis, haemorrhage and necrosis.	Compatible histology or CMV demonstrated in CSF by culture or DNA (by PCR)
CNS toxoplasmosis	Recent onset of a focal neurological abnormality or reduced level of consciousness AND response within 10 days to specific therapy.	Positive serum toxoplasma antibody AND (if available) single/multiple intracranial mass lesion on neuroimaging (CT or MRI)
HIV encephalopathy	Clinical finding of disabling cognitive and/or motor dysfunction interfering with activities of daily living, progressing over weeks or months in the absence of a concurrent illness or condition, other than HIV infection, which might explain the findings	Diagnosis of exclusion, and, if available, neuroimaging (CT or MRI)
Extrapulmonary cryptococcosis (including meningitis)	Meningitis: usually subacute, fever with increasingly severe headache, meningism, confusion, behavioural changes that respond to cryptococcal therapy	Isolation of *Cryptococcus neoformans* from extrapulmonary site or positive cryptococcal antigen test (CRAG) on CSF/blood

Grading of Clinical and Laboratory Toxicity

Estimating severity grade	Mild Grade 1	Moderate Grade 2	Severe Grade 3	Potentially life-threatening Grade 4
Clinical adverse event NOT identified elsewhere in the table	Symptoms causing no or minimal interference with usual social and functional activities	Symptoms causing greater than minimal interference with usual social and functional activities	Symptoms causing inability to perform usual social and functional activities	Symptoms causing inability to perform basic self-care OR medical or operative intervention indicated to prevent permanent impairment, persistent disability or death
Haemoglobin	8.0—9.4 g/dl OR 80—94 g/l OR 4.93—5.83 mmol/l	7.0—7.9 g/dl OR 70—79 g/l OR 4.31—4.92 mmol/l	6.5—6.9 g/dl OR 65—69 g/l OR 4.03—4.30 mmol/l	<6.5 g/dl OR <65 g/l OR <4.03 mmol/l
Absolute neutrophil count	1000—1500/mm^3 OR 1.0—1.5/G/l*	750—999/mm^3 OR 0.75—0.99/G/l*	500—749/mm^3 OR 0.5— 0.749/G/l*	<500/mm^3 OR <0.5/G/l*
Platelets	75000-99000/mm^3 OR 75—99/G/l*	50000—74999/mm^3 OR 50—74.9/G/l*	20000—49999/ mm^3 OR 20—49.9/ G/l*	<20000/mm^3 OR <20/G/l*

Chemistries	Mild Grade 1	Moderate Grade 2	Severe Grade 3	Potentially life-threatening Grade 4
Hyperbilirubinaemia	>1.0—1.5 x ULN	>1.5—2.5 x ULN	>2.5—5 x ULN	>5 x ULN
Glucose (fasting)	110—125 mg/dl	126—250 mg/dl	251—500mg/dl	>500 mg/dl
Hypoglycaemia	55—64 mg/dl OR 3.01—3.55 mmol/l	40—54 mg/dl OR 2.19—3.00 mmol/l	30—39 mg/dl OR 1.67—2.18 mmol/l	<30 mg/dl OR <1.67 mmol/l
Hyperglycaemia (nonfasting and no prior diabetes)	116—160 mg/dl OR 6.44—8.90 mmol/l	161—250 mg/dl OR 8.91—13.88 mmol/l	251—500 mg/dl OR 13.89—27.76 mmol/l	>500 mg/dl OR >27.76 mmol/l
Triglycerides	—	400—750 mg/dl OR 4.52—8.47 mmol/l	751—1200 mg/dl OR 8.48—13.55 mmol/l	>1200 mg/dl OR >13.55 mmol/l
Creatinine	>1.0—1.5 x ULN	>1.5—3.0 x ULN	>3.0—6.0 x ULN	>6.0 x ULN
AST (SGOT)	1.25—2.5 x ULN	>2.5—5.0 x ULN	>5.0—10.0 x ULN	>10.0 x ULN
ALT (AST)	1.25—2.5 x ULN	>2.5—5.0 x ULN	>5.0—10.0 x ULN	>10.0 x ULN
GGT	1.25—2.5 x ULN	>2.5—5.0 x ULN	>5.0—10.0 x ULN	>10.0 x ULN
Alkaline phos.	1.25—2.5 x ULN	>2.5—5.0 x ULN	>5.0—10.0 x ULN	>10.0 x ULN
Bilirubin	1.1—1.5 X ULN	1.6—2.5 x ULN	2.6—5.0 x ULN	>5 x ULN
Amylase	>1.0—1.5 x ULN	>1.5—2.0 x ULN	>2.0—5.0 x ULN	>5.0 x ULN
Pancreatic amylase	>1.0—1.5 x ULN	>1.5—2.0 x ULN	>2.0—5.0 x ULN	>5.0 x ULN

Lipase	>1.0−1.5 x ULN	>1.5−2.0 x ULN	>2.0−5.0 x ULN	>5.0 x ULN
Lactate	<2.0 x ULN without acidosis	>2.0 x ULN without acidosis	Increased lactate with pH <7.3 without life-threatening consequences	Increased lactate with pH <7.3 with life-threatening consequences
Gastrointestinal	Mild Grade 1	Moderate Grade 2	Severe Grade 3	Potentially life-threatening Grade 4
Nausea	Mild OR transient; reasonable intake maintained	Moderate discomfort OR intake decreased for <3 days	Severe discomfort OR minimal intake for ≥3 days	Hospitalization required
Vomiting	Mild OR transient; 2−3 episodes per day OR mild vomiting lasting <1 week	Moderate OR persistent; 4−5 episodes per day OR vomiting lasting ≥1 week	Severe vomiting of all foods/fluids in 24 hours OR orthostatic hypotension OR intravenous Rx required	Hypotensive shock OR hospitalization for intravenous Rx required
Diarrhoea	Mild OR transient; 3−4 loose stools per day OR mild diarrhoea lasting <1 week	Moderate OR persistent; 5−7 loose stools per day OR diarrhoea lasting ≥1 week	Bloody diarrhoea OR orthostatic hypotension OR >7 loose stools/day OR intravenous Rx required	Hypotensive shock OR hospitalization required

Respiratory	Mild Grade 1	Moderate Grade 2	Severe Grade 3	Potentially life-threatening Grade 4
Dyspnoea	Dyspnoea on exertion	Dyspnoea with normal activity	Dyspnoea at rest	Dyspnoea requiring O_2 therapy
Urinalysis	Mild Grade 1	Moderate Grade 2	Severe Grade 3	Potentially life-threatening Grade 4
Proteinuria				
Spot urine	1+	2+ or 3+	4+	Nephrotic syndrome
24-hour urine	200 mg to 1 g loss/day OR <0.3% OR <3 g/l	1 g to 2 g loss/day OR 0.3% to 1.0% OR 3 g to 10 g/l	2 g to 3.5 g loss/day OR >1.0% OR >10 g/l	Nephrotic syndrome OR >3.5 g loss/day
Gross haematuria	Microscopic only	Gross, no clots	Gross plus clots	Obstructive
Miscellaneous	Mild Grade 1	Moderate Grade 2	Severe Grade 3	Potentially life-threatening Grade 4
Fever (oral, >12 hours)	37.7—38.5 ^{0}C OR 100.0—101.5 ^{0}F	38.6—39.5 ^{0}C OR 101.6—102.9 ^{0}F	39.6—40.5 ^{0}C OR 103—105 ^{0}F	>40.5 ^{0}C OR >105 ^{0}F for ≥12
Headache	Mild; no Rx required	Moderate OR non-narcotic analgesia Rx	Severe OR responds to initial narcotic Rx	Intractable
Allergic reaction	Pruritus without rash	Localized Urticarial	Generalized urticaria, angioedema	Anaphylaxis
Rash hypersesnitivity	Erythema, pruritus	Diffuse maculopapular rash OR dry desquamation	Vesiculation OR moist desquamation OR ulceration	ANY ONE OF: mucous membrane involvement, suspected Stevens-Johnson (TEN), erythema multiforme, exfoliative dermatitis
Fatigue	Normal activity reduced by <25%	Normal activity reduced by 25—50%	Normal activity reduced by >50%; cannot work	Unable to care for self

Source: Division of AIDS, National Institute of Allergy and Infectious Diseases, version 1.0 December 2004, clarification August 2009.

NOTE: This clarification includes the addition of Grade 5 toxicity, which is death.

For abnormalities not found elsewhere in the toxicity table, use the information on *Estimating severity grade* in the first column

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 provides a summary of some features of each ARV drug. The second table (gives an overview of ARV side effects. Following the tables, each ARV drug is listed with discussion of its side effects).

Table 18: 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	TB/HIV co-infection
NRTI							
Zidovudine (ZDV or AZT)	300mg (one tablet) twice per day; 250 mg twice daily if <40 kg	Only available as part of FDC (60 and 300 mg)	No	None	No change necessary	Preferred	Preferred
Stavudine (d4T)	30mg (one capsule) twice per day	Only available as part of FDC (6, 12,15, and 30 mg FDC)	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	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	No	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	Contraindicated if prior renal disease; 300 mg daily for GFR>50 ml/min. 300 mg every 48 hours for patients with GFR 40-49. Do not give to patients with renal impairment (CrCl < 30ml/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	Tablet 50 mg; Capsule 200 mg; Capsule 600mg	No	Avoid taking with high fat meal	Renal: no change necessary Hepatic: consider alternative drug	No	Preferred
PI							
Lopinavir + ritonavir (LPV/r)*	400mg/100mg (two 200mg/50mg tablets) twice per day (co-formulated); 400mg/400mg twice per day if on Rifampicin for TB by adding 3 RTV 100 mg tablets to each dose. If RTV 100 mg tablets not available, double standard LPV/r dosing up to two weeks after Rifampicin therapy	Tablet 200mg + 50mg; Tablet 100 mg +25 mg; Oral solution, 80mg/ml + 20mg/ml	Yes; stable for 3 months at room temperature	Take with food	Renal : no data Hepatic : Avoid	No	No
Atazanavir + ritonavir (ATV/r) **	300mg (one tablet) and 100mg (one tablet) taken together once per day or Fixed Dose Combination of ATV 300mg + RTV 100mg (one tablet, co-formulated) once per day	Single formulations ATV 300mg and RTV 100mg; FDC Co-formulated Tablet 300mg + 100mg	Yes	Take with food	No data[1]	Yes	No

**Atazanavir+ritonavir (ATV/r: 300mg/100mg) is well-tolerated and has comparable efficacy to Lopinavir + ritonavir. ATV/r will be available in Cambodia 2012 in both single (one tablet of ATV 300mg + one tablet RTV 100mg) and Fixed Dose Combination (one combined tablet of ATV 300mg/RTV 100mg) formulations. Seek expert advice in the event of hepatitis or renal impairment in second line patients.

Combination							
Zidovudine + lamivudine (AZT + 3TC)	300mg/150mg (one tablet) twice per day	300 mg/150 mg and 60 mg/30mg	No	None	Use individual formulations if CrCl < 50ml/min	Preferred	Preferred
Stavudine + lamivudine (d4T + 3TC)	30mg/150mg (one tablet) twice per day	30 mg/150 mg and 12 mg/60 mg	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	30 mg/150mg/200 mg; 12 mg/60mg/100 mg	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	300mg/150mg/200mg; 60mg/30mg/50 mg	No	None	Renal : Use individual formulations if CrCl < 50ml/min Hepatic : Avoid	Preferred	Avoid if possible as overlapping toxicity and dosing is not clear

* All doses for ARVs are based on international standards.

Table 19: 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'
Anemia	AZT	Weakness, lethargy, dizziness	Check CBC at baseline. Avoid AZT if Hb<9.5g/dl.	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, ATV	Jaundice	Nil	**After ruling out other causes of hyperbilirubinemia (eg hepatitis, hemolysis) switch PI**
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)	Stop ARVs, support patient, restart non d4T or ddi regimen when stable
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, ATV/r, 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>$750x10^3$/l: check CBC again in 2-4 weeks. Neutrophil count<$750x10^3$/l: cease AZT
Pancreatitis	ddI, d4T	Nausea, vomiting, abdominal pain	Avoid ddI, d4T if risks for pancreatitis	Check amylase. Cease drug if amylase > 1.5 ULN 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
Severe Life Threatening 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 all drugs. Do not rechallenge
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.

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 20 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 dyspnea.

- 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 TFV 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 20: 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 FTC 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
- ddI should be used with caution with TDF as it can increase ddi levels; dosing of ddi should be reduced to 250 mg a day
- ddi levels can also increase 100% with ganciclovir. Patients on both drugs should be monitored closely

Abacavir (ABC)

- The major side effect of ABC is hypersensitivity syndrome. It occurs in 3-5% of Caucasians and significantly less in Southeast Asian users but 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.

Tenofovir (TDF)

- TDF is classified as an nucleotide reverse transcriptase inhibitor but functions as an NRTI equivalent in ART regimens. It 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.

Figure 1: ddI associated pancreatitis:

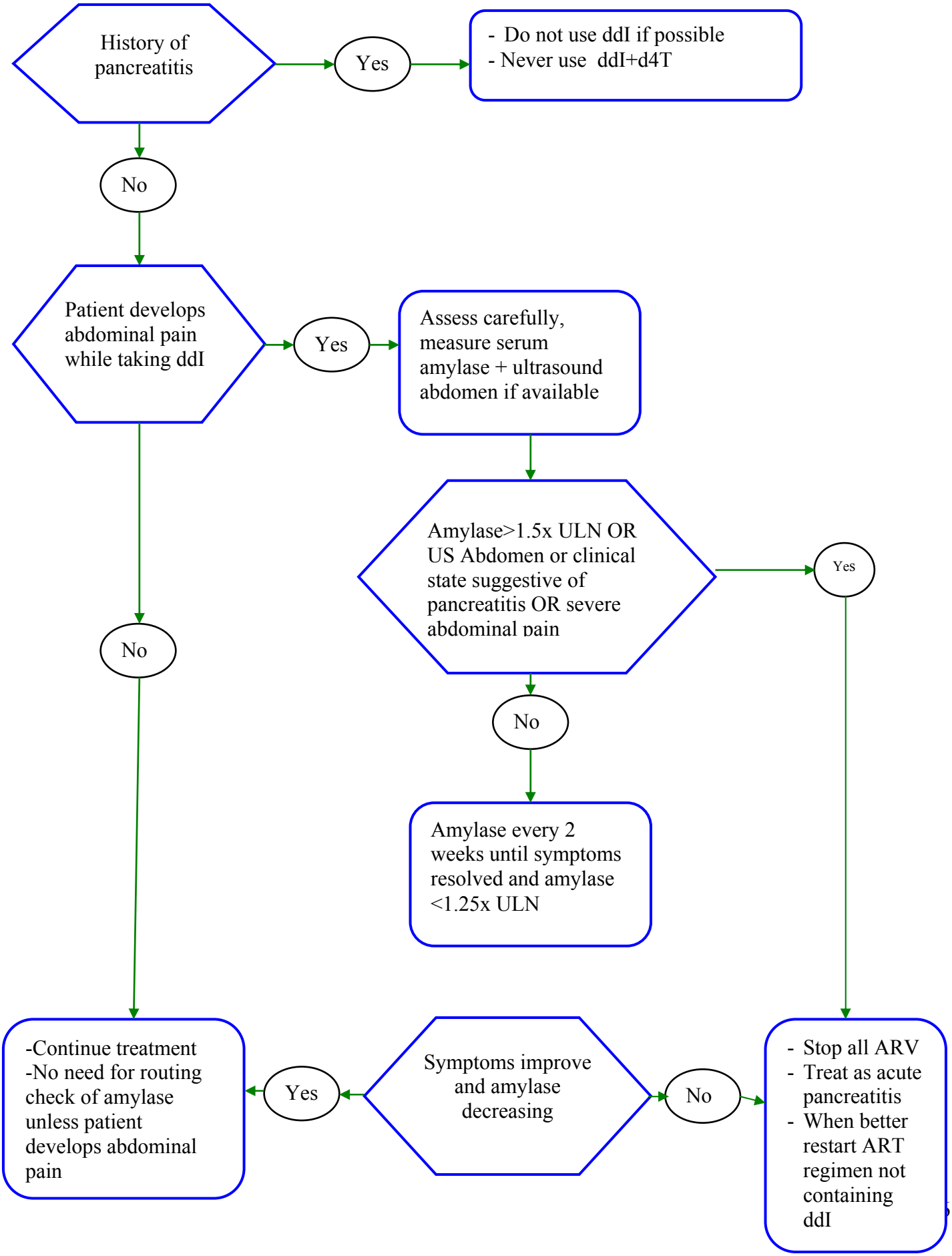


Figure 2: AZT-associated anemia

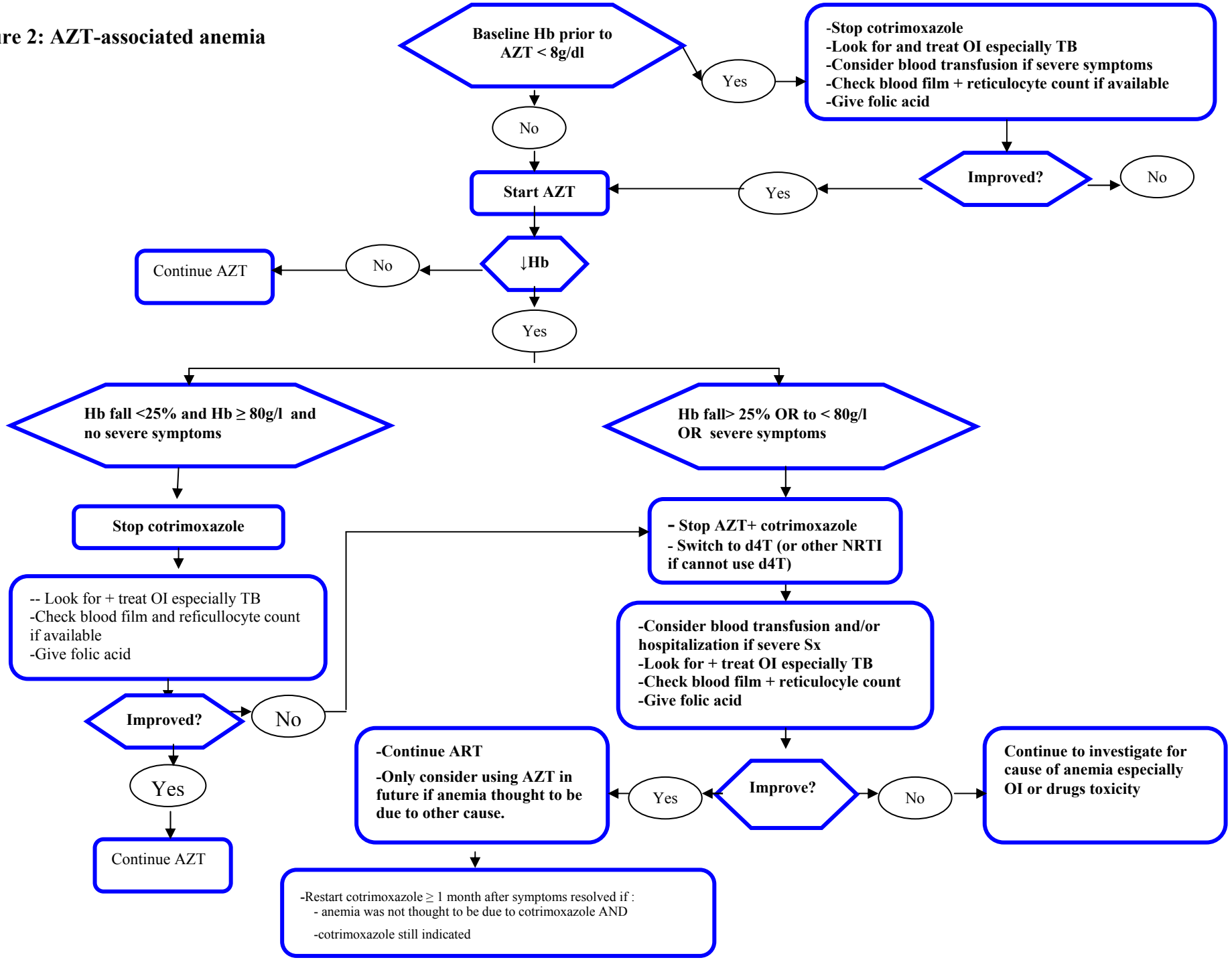
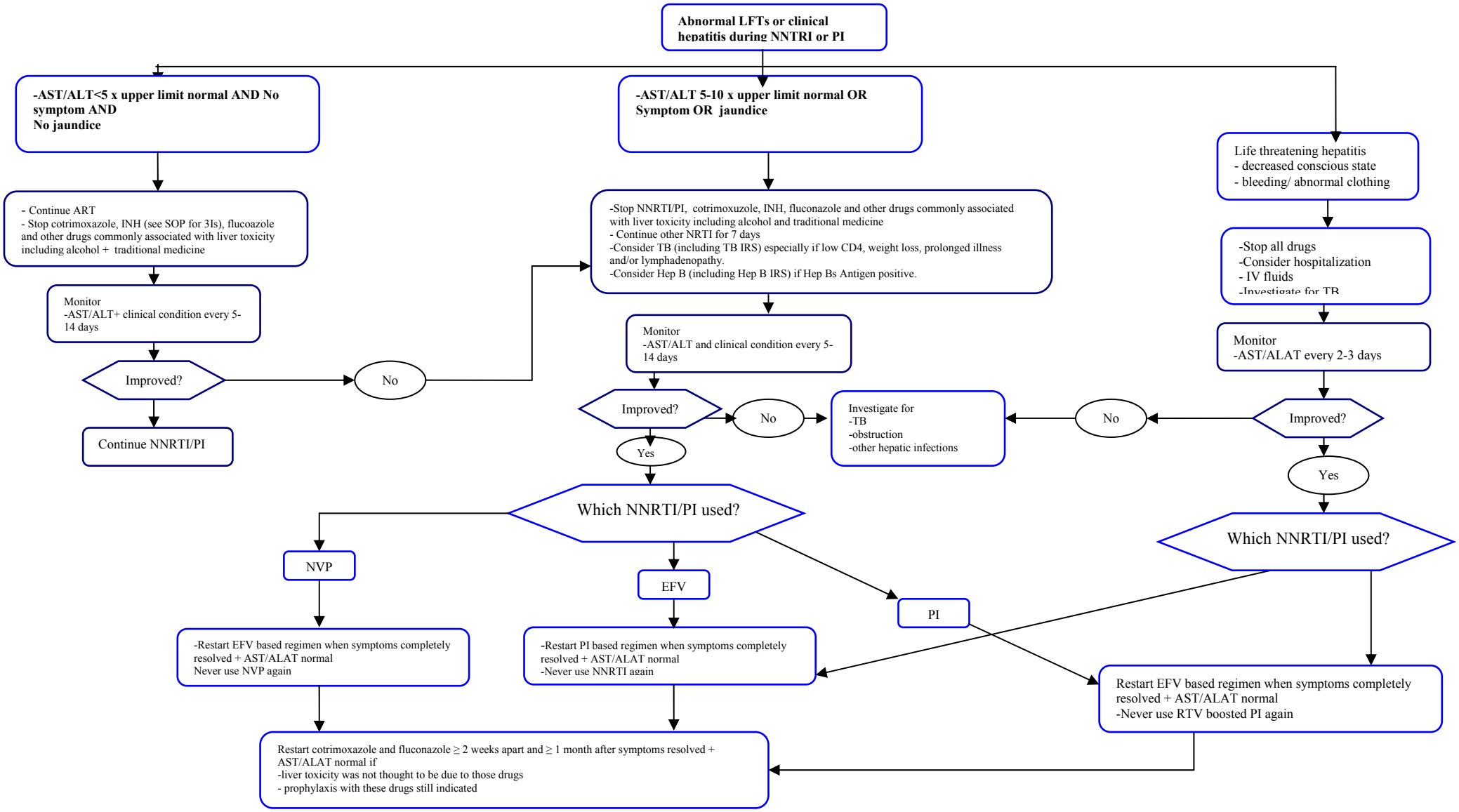


Figure 3: ART-Associated liver toxicity



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. 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.

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 rash without other symptoms or mucosal involvement occurs, NVP can be continued with careful observation. During the low dose NVP initiation period, do not increase the dose of NVP until the rash has resolved. If rash does not resolve in one month, switch to EFV.
- If moderate rash, switch NVP to EFV.
- If any of the following are present, stop all ARVs and cotrimoxazole. NVP should be permanently ceased and neither NVP or EFV given in the future (use PI when symptoms resolve):
    - 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.
- EFV is also teratogenic and should not be given during pregnancy, particularly during the first trimester.

Figure 4: NRTI-Associated Rash

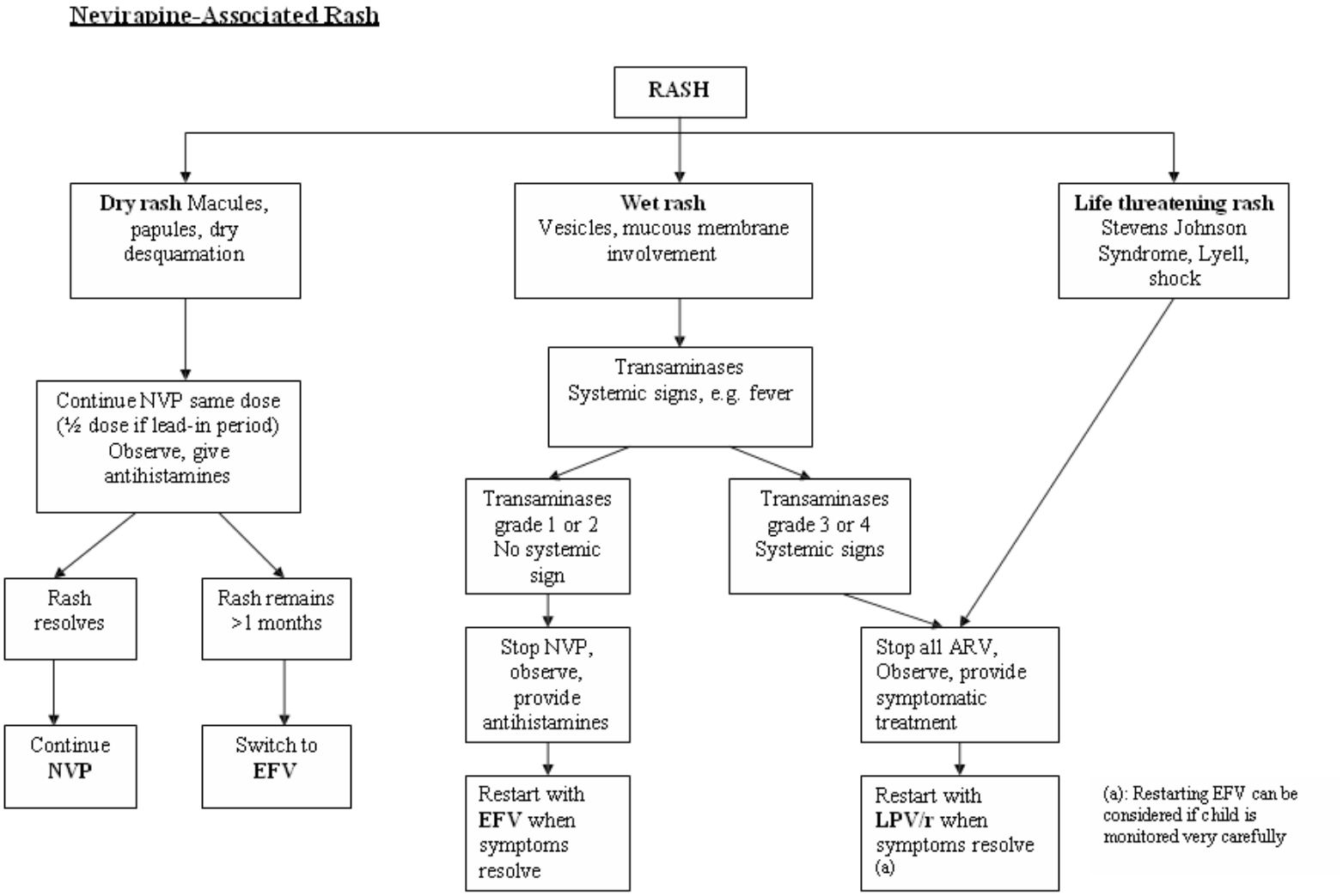
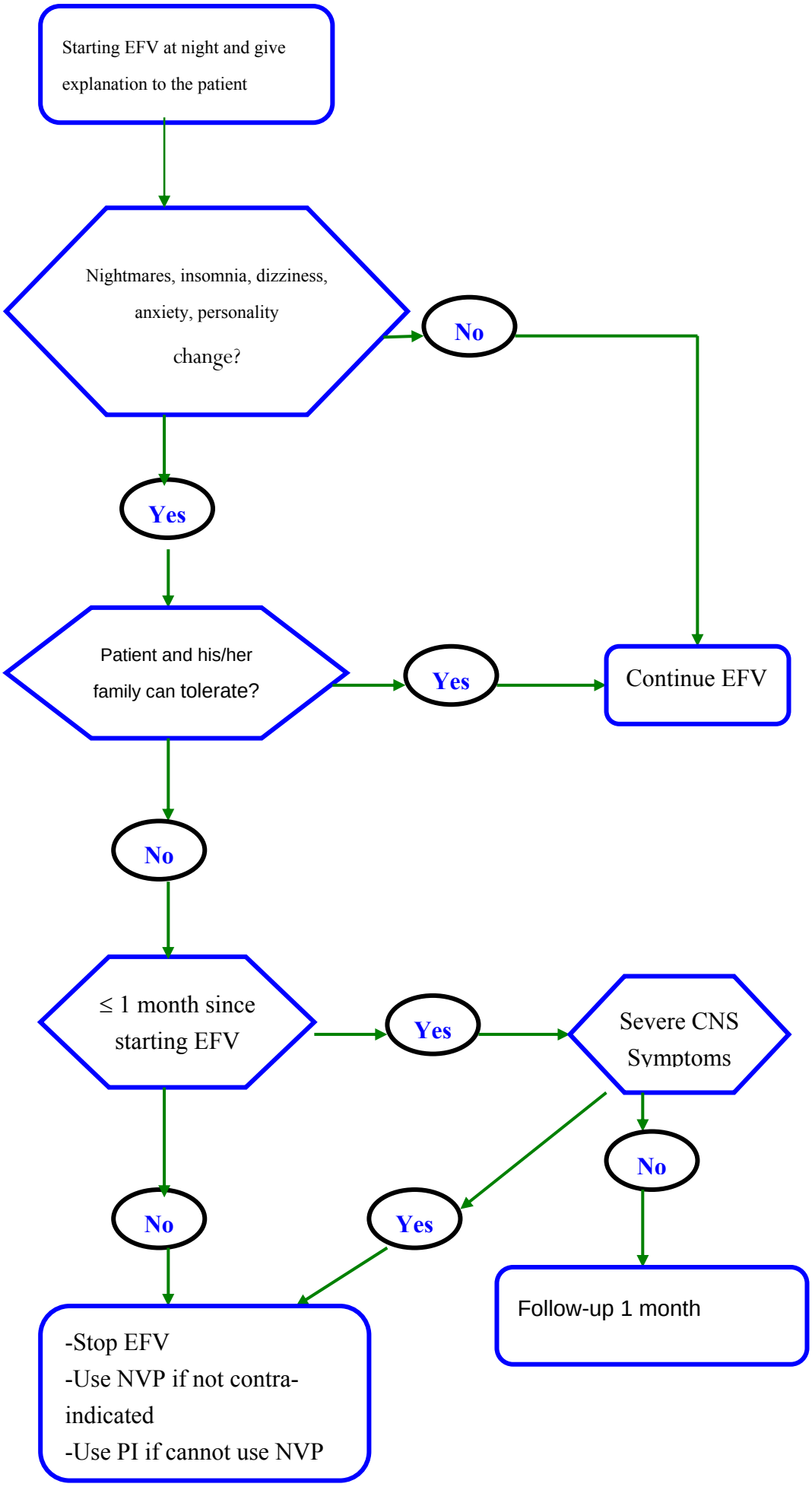


Figure 5: EFV-associated CNS symptoms



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, hyperglycemia 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 hyperglycemia/diabetes. Studies are ongoing, but metformin is probably the best first line treatment. If severe or difficult to control, PIs should be ceased. Hyperglycemia 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 hyperlipidemia 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.

Lopinivir/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.

Annex 3: Important ARV drug interactions

There are many complicated interactions between ARVs and other drugs. Table 21 gives an overview of major drug interactions. There are many more druginteractions that are not listed in this table. Always check reference texts for interactions before prescribing new drugs. http://www.hiv-druginteractions.org is also an excellent source of information.

Table 21: Common Drug Interactions with NVP, EFV, and LPV/r

Interacting drug	NVP	EFV	LPV/r
Ketoconazole	X	+/-	
Itraconazole	Can affect concentration of both NVP and itraconazole. Adjust dose of both		Decreased metabolism, ketoconazole concentration increased. Use with caution ketaconazole doses>200 mg/day
Fluconazole	May cause ↑ NVP Level		OK
Rifampicin	Increased metabolism, significant decrease in NVP levels	May increase EFV to 800mg/d	Increased metabolism, significant decrease in PI levels
Clarithromycin	May decrease clarithromycin levels	May decrease clarithromycin levels	Dose reduction of clarithromycin needed if renal failure
Oral contraceptive[1]	X	X	X
Methadone	Decreased methadone concentration. Increase methadone dose to effect	Decreased methadone concentration. Increase methadone dose to effect	Decreased methadone concentration. Increase methadone dose to effect
'Statins'[2]	+/-	+/-	X
SSRI Antidepressants	+/-	+/-	May cause ↑ SSRI level. Start at lowest dose
Anti-epileptic drugs[3]	X	X	X
Benzodiazepines[4]	X	X	X
Other drugs that should not be co-administered	Garlic supplements	Astemizole Terfenadine Cisapride Midazolam Triazolam Ergotamine Dihydro-ergotamine Garlic	Astemizole Terfenadine Cisapride Midazolam Ergotamine Dihydro- ergotamine Garlic Flecanide Pimozide Garlic
Miscellaneous	Can lower steroid levels	Monitor warfarin if co-administered	

[1]**Additional or alternative methods of contraception should be used. Medroxyprogesterone Depot generally effective but should always be used with barrier precautions.**

[2]Pravastatin or fluvastatin can be used at the normal dose. Simvastatin must never be used.

[3]Levels of carbamazepine are increased, phenytoin decreased. Valproate is preferred in this situation.

[4]Diazepam and midazolam levels increased significantly, may cause life-threatening over-sedation. Use lorazepam if possible.

Annex 4: Viral Load Testing Strategy

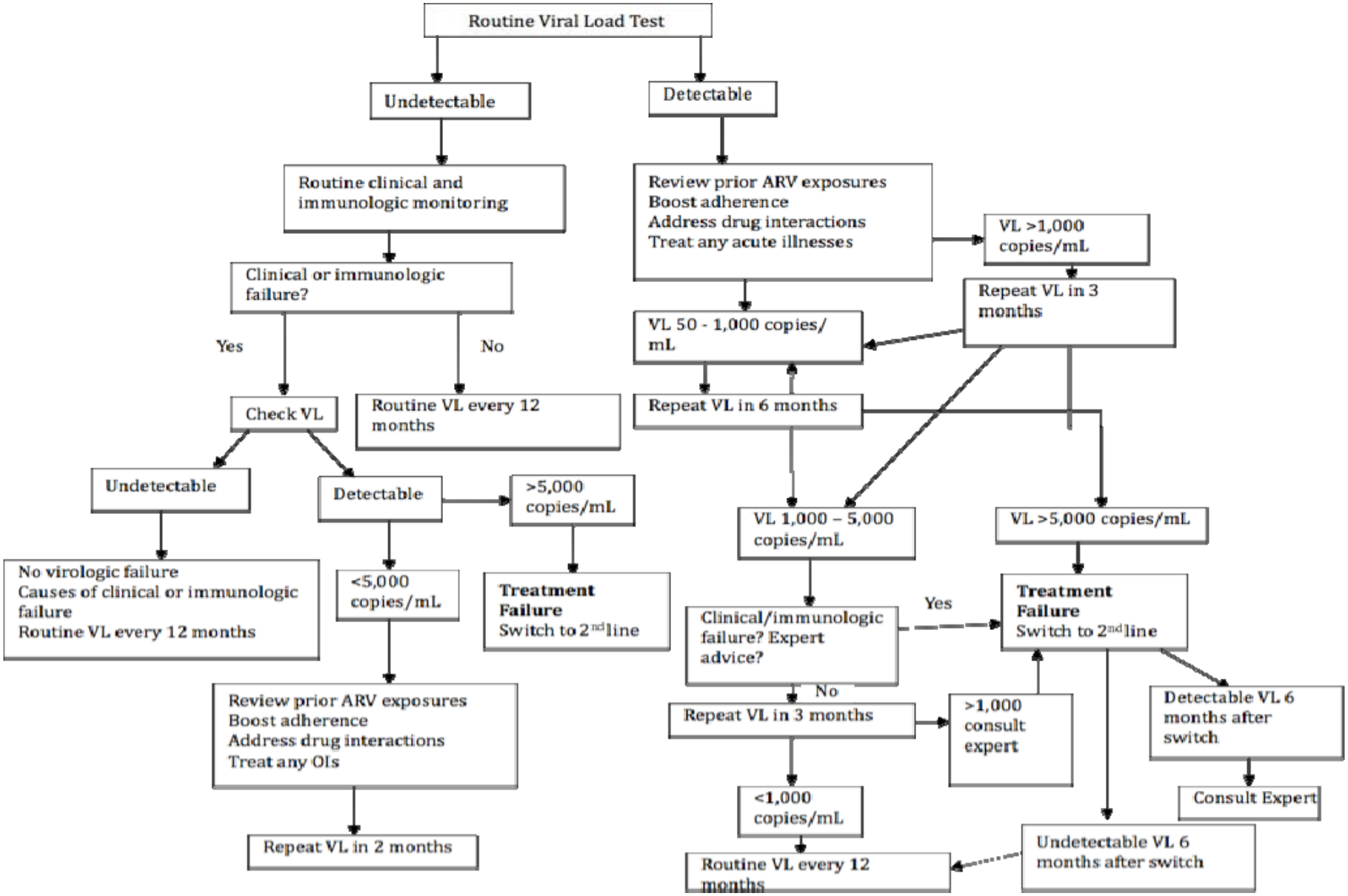
In certain circumstances, you may need to convert copies/ml to a log scale to address treatment failure.

Table 22: Conversion of viral copies/ml and log

Copies/ml	Log
400	2,6
1,000	3,0
10,000	4,0
20,000	4,3
30,000	4,5
50,000	4,7
100,000	5,0

A significant change between two VL measurements from the same patient is defined as a 3 fold difference (+/-0.5 Log). The following algorithm

Figure 6: Routine Viral Load Algorithm



Annex 5: Karnofsky Performance Scale

Table 23: 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

Annex 6: ARV Prophylaxis for Pregnant Women

Table 24: ART and ARV Prophylaxis Regimens for HIV-infected Women and for HIV-exposed Infants

<table>
<tr><th>Course</th><th>Antenatal</th><th>Labour and Delivery</th><th colspan="2">Postnatal</th></tr>
<tr><td rowspan="2">Maternal ART

CD4 ≤ 350 cells/mm³</td><td rowspan="2">Mother:
either AZT[2] + 3TC + NVP[3]
or
AZT + 3TC + EFV[4]
start as soon as possible irrespective of gestational age</td><td rowspan="2">Mother:
either AZT + 3TC + NVP
or
AZT + 3TC + EFV</td><td colspan="2">Mother:
Continue ART lifelong for her own health</td></tr>
<tr><td colspan="2">Infant: daily NVP given for 6 weeks (irrespective of feeding method) start as soon as possible after birth (within 6-12 hours)
Dose: Birth weight ≥ 2500g 15 mg[5] oral suspension once daily
Birth weight < 2500g 10 mg[18] oral suspension once daily</td></tr>
<tr><td rowspan="2">Maternal Triple ARV Prophylaxis

CD4 > 350 cells/mm³</td><td rowspan="2">Mother:
AZT[15] + 3TC + EFV[17]
start at 14 weeks gestation or as soon as possible thereafter</td><td rowspan="2">Mother:
AZT + 3TC + EFV</td><td>Mother Breastfeeding:
Continue AZT + 3TC + EFV[6] until 1 week after complete cessation of breastfeeding
Stop EFV when breastfeeding stops, then stop AZT + 3TC one week later[7]</td><td>Mother Replacement Feeding:
Stop ARV Prophylaxis as follows:
Stop EFV after delivery, then stop AZT + 3TC one week later[20]</td></tr>
<tr><td colspan="2">Infant: daily NVP given for 6 weeks (irrespective of feeding method) start as soon as possible after birth (within 6-12 hours)
Dose: Birth weight ≥ 2500g 15 mg oral suspension once daily
Birth weight < 2500g 10 mg oral suspension once daily</td></tr>
<tr><td colspan="3">MATERNAL ARV DOSAGES</td><td colspan="2"></td></tr>
<tr><td>AZT + 3TC + NVP</td><td colspan="4">300 mg / 150 mg / 200 mg (1 tablet twice/day)</td></tr>
<tr><td>AZT + 3TC + EFV</td><td colspan="4">AZT + 3TC: 300 mg / 150 mg (1 tablet twice/day)
EFV: 600 mg (1 tablet once/day)</td></tr>
</table>

[2] If the woman is anaemic (Hb ≤ 7 g/dl) do not use AZT, use d4T instead (or use TDF + 3TC + EFV) and ensure the anaemia is treated

[3] It is important not to initiate NVP in women with high CD4 counts (> 350 cells/mm³) due to an increased risk of hepatotoxicity

[4] Do not use EFV in the 1st trimester, use NVP instead (there may be a risk of teratogenicity if EFV is used in the 1st trimester)

[5] 15 mg Nevirapine suspension = 1.5 ml, 10 mg = 1.0 ml

[6] Women must be carefully counselled about the importance of using effective contraception to avoid conception while taking EFV postnatally

[7] To reduce the chance of resistance developing to EFV due to its longer half life

Table 25: ARV Drugs for Women diagnosed with HIV Infection during Labour or immediately Postpartum

Course	Antenatal	Labour and Delivery	Postnatal
Mother diagnosed with HIV infection during labour **or** **Mother received no ARVs during pregnancy**		**Mother**: Single dose NVP 200 mg as soon as possible in labour and AZT + 3TC twice daily	**Mother:** Continue AZT + 3TC twice daily[8] for 7 days after birth Inform OI/ART about the newly diagnosed mother and draw blood for CD4 testing[9] before mother is discharged. Arrange follow-up appointment for the mother at OI/ART at 6 weeks after delivery **Infant: daily NVP given for a minimum of 6 weeks[10]** start as soon as possible after birth (within 6-12 hours) **Dose:** Birth weight ≥ 2500g 15 mg oral suspension once daily Birth weight < 2500g 10 mg oral suspension once daily
Mother diagnosed with HIV infection immediately postpartum			**Mother:** Inform OI/ART about the newly diagnosed mother and draw blood for CD4 testing[22] before mother is discharged. Arrange follow-up appointment for the mother at OI/ART at 6 weeks after birth **Infant: daily NVP given for a minimum of 6 weeks[23]** start as soon as possible after birth (within 6-12 hours) **Dose:** Birth weight ≥ 2500g 15 mg oral suspension once daily Birth weight < 2500g 10 mg oral suspension once daily
MATERNAL ARV DOSAGES			
NVP	200 mg, give one dose only		
AZT + 3TC	300 mg / 150 mg (1 tablet twice/day)		

[8] To reduce the chance of developing resistance to NVP

[9] If **CD4 ≤ 350 cells/mm³**, mother needs lifelong ART for her own health. CBOs should be contacted to ensure that mother is seen at OI/ART as soon as possible so that ART can be initiated. If **CD4 > 350 cells/mm³,** the infant must continue daily NVP until 1 week after complete cessation of breastfeeding

[10] If the mother is breastfeeding, infant prophylaxis should be continued until 1 week after complete cessation of breastfeeding. If the mother is replacement feeding, the infant prophylaxis can be stopped 6 weeks after delivery

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