



**ANTIRETROVIRAL THERAPY
FOR
CHRONIC HIV INFECTION
IN
ADULTS AND ADOLESCENTS**

New ART Protocols

MAY 2007

Foreword and Acknowledgements

This document is provided with the aim of standardizing high quality HIV care in all the sectors of health. The document provides health care workers with a knowledge base that will assist in providing appropriate treatment for patients with HIV. The health care giver is further encouraged to refer to other more extensive literature on the subject. The new protocols presented here are based on evidence from documented long term studies, experiences of a large number of clinicians both local and international, global recommendations from WHO and other international research institutions.

The Ministry of Health is grateful for the support rendered to the NAC HIV Treatment Working Group that set out to develop these guidelines. Many thanks to the following institutions' dedicated staff and individuals:

- U.S. Centers for Disease Control and Prevention (CDC)
 - Clinton Foundation HIV/AIDS Initiative (CHAI)
 - Centre for Infectious Disease Research in Zambia (CIDRZ)
 - Churches Health Association of Zambia (CHAZ)
 - Faculty of General Practitioners and Private Sector (FGP)
 - Johns Hopkins Program for Information and Education on Gynaecology and Obstetrics (JHPIEGO)
 - Japanese International Cooperation Agency (JICA)
 - John Snow Inc. /Deliver (JSI/Deliver)
 - National HIV/AIDS/STI/TB Council (NAC)
 - School of Medicine, University of Zambia (SOM, UNZA)
 - University Teaching Hospital (UTH)
 - World Health Organisation (WHO)
 - Zambia HIV/AIDS Prevention, Care and Treatment Partnership (ZPCT)
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ANTIRETROVIRAL THERAPY FOR CHRONIC HIV INFECTION IN ADULTS AND ADOLESCENTS

GENERAL PRINCIPLES

Taking Antiretroviral (ARV) therapy requires a long-term commitment from the patient. Correct and consistent use is required for the drugs to be effective. Antiretroviral drugs (ARVs) have side effects that can make them difficult for some patients to take. Thus the decision about when to start therapy is an important one. Treating someone too early may lead to unnecessary toxicity and premature development of drug resistance, while treating too late can increase the risk of morbidity, mortality, and treatment failure.

Goals of Therapy

- Reduction of viral load as much as possible for as long as possible
- Restoration and/or preservation of immunologic function
- Improvement of quality of life
- Reduction of HIV-related illness and death
- Possible reduction in transmission to others

General principles of ARV therapy

- Use of combinations of at least three ARV drugs
- Maximize adherence to the ARV regimen
- Rational sequencing of ARV drugs
- Avoiding Resistance

Prerequisites for administration of ARV therapy

- Appropriate drugs are available
- Drug supply can be sustained
- Basic clinical and laboratory measures are used to determine need for treatment
- Basic clinical and laboratory measures are available to monitor for toxicity
- The patient understands the importance of near-perfect adherence
- Health care providers have been trained in the use of ARV therapy

Highly Active Antiretroviral Therapy

Highly Active Antiretroviral Therapy (HAART) consists of a combination of at least three drugs: namely, any of the following three combinations

- 2 Nucleoside Reverse Transcriptase Inhibitor (NRTI) + 1 Non Nucleoside Reverse Transcriptase Inhibitor (NNRTI)
- 2 NRTI + 1-2 Protease Inhibitors (PI)
- 3 NRTI

General Points

- The goal of the above combinations is to reduce the viral load to undetectable levels.
- HAART needs to be taken for the rest of the patient's life.
- Adherence to medication is vital to prevent emergence of resistant strains of HIV.
- Although the short-term side effects of HAART are well documented, long-term effects are less clear.
- HAART is indicated for any patient who meets the Zambian National Guideline eligibility criteria.
- All patients must have a confirmed HIV serology test and should access counselling services.
- HAART complements the treatment and prophylaxis of opportunistic infections.
- HAART is not an emergency and it has to be initiated after a proper treatment preparation
- In the case of post exposure prophylaxis (PEP), prophylaxis should be initiated as soon as possible (ideally within two hours of exposure)
- In PMTCT more urgent prophylaxis needs to be considered to optimize PMTCT efforts

Who should prescribe HAART?

Health care providers who fulfill the following requirements

- Legally recognized to prescribe in Zambia
- Trained in HIV/AIDS management
- Has access to sustainable drug supply and to facilities to monitor therapy
- Participates in the continuous medical education in the use of ARVs and monitoring of ART

How to Clinically Stage HIV Disease?

Clinical Staging of HIV disease based on WHO criteria (2006)
See Annex for WHO Clinical Staging of HIV Disease in Adults and Adolescents

Zambian Recommendations for initiating antiretroviral therapy in adults and adolescents with documented HIV infection

Clinical Stage	CD4 available	CD4 not available
I	CD4 guided	Do not treat
II	CD4 guided	Total Lymphocyte Count <1200*
III	Treat**	Treat
IV	Treat	Treat

* CD4 count strongly recommended
** If CD4 between 200-350, also treat if there is more than one Stage 3 sign or repeated Stage 3 problem (if has active TB, see below)

CD4 criteria for initiation of ART

CD4 (cell/mm)	Actions
<200	Treat irrespective of clinical stage
200-350	Treat if there is more than one Stage 3 sign or repeated Stage 3 problem* (for pregnancy and TB see appropriate section)
>350	Defer treatment

* For others - monitor more frequently and consider treatment based on clinical or immunologic deterioration. Always start well before CD4 decreases to below 200
Note: Measure CD4 after stabilization of any inter-current illness

**ART Initiation
(ARV Dosing Guideline in Annex)**

Considerations before starting ARV therapy

- Effectiveness of regimen
- Potential for serious adverse effects and toxicity
- Side effects and tolerability
- Potential for interactions with other drugs
- Potential for treatment options should the initial drug combination fail
- Cost and availability
- Patient readiness and likelihood of adequate adherence
- Presence of pregnancy or the risk of becoming pregnant
- Presence of tuberculosis and other illnesses -anemia, peripheral neuropathy, kidney disease, hepatitis
- Ability of the patient to return for regular and reliable follow-up

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Recommended regimens

(For patients initiating therapy up to the new 2007 guidelines)

The choice of the ARV regimen should be within Zambian National Guidelines whenever possible.

First Line Regimens			Second Line Regimens		
NRTI	NRTI	NNRTI	NtRTI	NRTI	PI
AZT	3TC	EFV	TDF	FTC ¹	LPV/r ²
or d4T		or NVP ³	(Preferred) ABC (Alternative if there is renal insufficiency)	ddI ⁴	LPV/r ²
<p>¹ Lamivudine (3TC) or Emtricitabine (FTC) is continued in the second line regimen because their resistance mutations decrease viral replication capacity, increase HIV susceptibility to Tenofovir (TDF) and AZT</p> <p>² If unable to tolerate LPV/r then refer to HIV Specialist for additional options</p> <p>³ For women who have had exposure to nevirapine within 6 months for PMTCT, do not use a nevirapine containing regimen</p> <p>⁴ 3TC resistance reduces efficacy of ABC, therefore ddI will be substituted for 3TC</p>					

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New Recommended regimens
Based on new availability of TDF/FTC +/- EFV as fixed dose combination which can be given once daily; proven potency of TDF; more favourable mutation pathway; lower incidence of anaemia

(For patients initiating therapy after the new 2007 guidelines)

First Line Regimen			Second Line Regimen		
TDF*	FTC	EFV or NVP ³	AZT ¹ or d4T ⁴	3TC ² or TDF/FTC ⁵	LPV/r ⁶
* TDF has been associated with renal toxicity: if CrCl <50 ml/min , initiate therapy with ABC/3TC					
¹ AZT/3TC/LPV/r is preferred second line regimen for patients failing Tenofovir based first line. ² Lamivudine (3TC) or Emtricitabine (FTC) are continued in the second line regimen because their resistance mutations decrease viral replication capacity, increase the HIV susceptibility to Tenofovir (TDF) and AZT ³ For women who have had exposure to nevirapine within 6 months for PMTCT, do not use a nevirapine containing regimen ⁴ Stavudine (d4T) is associated with long term toxicity and should only be used in the second line if AZT cannot be taken ⁵ TDF mutations can increase HIV susceptibility to AZT and may increase AZT efficacy, while TDF may maintain some activity ⁶ If unable to tolerate LPV/r then refer to HIV Specialist for additional options					

PRACTICAL HINTS TO AID IN CHOOSING A SPECIFIC REGIMEN:

- Initiation of a regimen containing AZT may worsen anemia because of bone marrow suppression. It is not recommended to start AZT with hemoglobin less than 10 gm/dl. ARV therapy should be delayed until the anemia has been treated or an alternative NRTI combination should be started in this situation.
- Patients with symptoms of peripheral neuropathy (numbness, tingling, or burning sensations in the extremities) and those also being treated with isoniazid (INH) should not be started on a d4T-containing regimen, since this may worsen their symptoms.
- Women with CD4 > 250 cells/mm³ have been associated with a higher incidence (11%) of symptomatic hepatotoxicity when treated with NVP; NVP-containing ART regimens initiation should be avoided in women who are pregnant or at risk for pregnancy with CD4 > 250 cells/mm³
- Use of single-dose NVP for perinatal prophylaxis has not been associated with hepatotoxicity
- A two-week lead-in NVP dose (200mg once daily) before increasing to full dose (200 mg twice daily) may reduce risk of skin rash and/or hepatotoxicity
- EFV has been associated with serious birth defects; avoid EFV use in women of reproductive age who are not using effective and consistent contraception or trying to get pregnant or who are in the 1st trimester of pregnancy
- EFV is associated with CNS side effects (drowsiness, insomnia, abnormal dreams, impaired concentration, etc); these generally occur with the first few doses and usually diminish or disappear after 2-4 weeks. Avoid with severe untreated psychiatric illness
- EFV is the recommended NNRTI with TB co-infection and treatment with rifampicin
- Consider potential drug-drug interactions or additive toxicity if initiating ART in patients on certain other drugs (e.g. INH and d4T(peripheral neuropathy); cotrimoxazole and NVP or EFV (skin rash); cotrimoxazole and AZT (bone marrow suppression); INH and NVP or EFV (hepatotoxicity). In these situations may consider alternate ARV agent or close clinical and/or laboratory monitoring
- Patients with HIV-2 instead of HIV-1 are not effectively treated with the NNRTI class of drugs (NVP or EFV): use a PI based regimen
- With decreased Creatinine Clearance there is need for dose adjustment for TDF, 3TC, FTC, and d4T; AZT only with "severe" renal impairment or patient on dialysis (refer to Table below)

SPECIAL CONSIDERATIONS DURING TRANSITION PERIOD:

- Continue stable patients without signs of toxicity or clinical failure on current regimen (AZT or d4T + 3TC + NVP or EFV)
- Switch patients with signs of toxicity, but not clinical failure, to proposed first line regimen (TDF/FTC + NVP or EFV)
- Switch patients with signs of clinical failure on current regimen to new proposed second line (TDF/FTC + LPV/r)
- Pediatric patients who are transitioning to adult care follow the above recommendations for stable patients, patients with toxicity, and patients with clinical failure
- Patients outside of new protocol will be transitioned to new second line regimen as follows:
 - TDF+ddI+LPV/r should be switched to TDF/FTC+LPV/r
 - ABC+ddI with either LPV/r or NFV should be switch to TDF/FTC+LPV/r unless renal insufficiency present
 - TDF+ddI+NFV should be switched to TDF/FTC+LPV/r
 - d4T/3TC+IDV or AZT/3TC+IDV should be switched to TDF/FTC+LPV/r
 - d4T/3TC+ABC or AZT/3TC/ABC consult with Provincial HIV Specialist for transition
 - d4T/3TC+LPV/r or AZT/3TC+LPV/r consult with Provincial HIV Specialist for transition

ADHERENCE TO HAART

- Good adherence means
 - Drugs should be taken at the same time of the day to maintain constant drug blood level.
 - Taking all the medications at the right time, in correct doses, with or without food (if indicated)
 - Not skipping doses or starting and stopping therapy
- NNRTIs have a low genetic barrier to resistance and near-perfect adherence is essential to prevent development of resistance and ultimately treatment failure
- Give written dosing instructions to patients
- Provide one-on-one counseling to each patient
 - This often takes several counseling sessions before a patient is truly “ready” to start ART
 - This should include information about drug-related side effects: how to recognize serious adverse effects, when to seek care and how to prevent or manage mild side effects
- Encourage patients to identify treatment supporters (family members, buddies) and include them in counseling
- Find ways to help patients overcome obstacles, such as disclosure
- Link patients with adherence support groups
- Counsel patients to avoid drug abuse and to refrain from excessive alcohol use
- All patients should be given information about how and when to contact their health care provider
- Assess adherence at every visit to the clinic:
 - It is critically important to assess how the patient is taking his or her drugs at each visit
 - An assessment, with open ended and targeted questions and using other tools (e.g. pill counts) should be done at each visit to the clinic
- Assess adherence at every contact with an adherence support worker or home-based care giver
 - Patients with suspected or identified adherence problems need to be referred to the ART care team immediately

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- Assessing adherence is not a simple question and patients are unlikely to volunteer information about non-adherence
 - Ask how the patient is taking the medications prescribed
 - Probe, verify, ask follow-up questions
 - Find out what the barriers are and help the patient to find ways to overcome these barriers
 - Pill counts can be helpful

BASELINE EVALUATION AND MONITORING ARV THERAPY

Before initiation and after starting on ARV therapy, it is critical that the patient receive regular laboratory and clinical monitoring and follow-up. The purpose of monitoring and follow-up is to:

- assist in choice of initial regimen
- assess effectiveness of therapy
- evaluate potential side effects or toxicity from ARV therapy
- assess and re-enforce adherence to therapy
- evaluate for the development of other HIV-related illnesses

Some patients may need to be seen more often than others, because of side effects, difficulty with adherence, or for other reasons. The healthcare provider should be flexible according to the needs of the individual patient. The minimum recommended timing and frequency of follow-up is outlined in the table below.

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Timeline	Clinical	Laboratory	Other
Baseline	<ul style="list-style-type: none"> -Complete History & Physical (including ART history, current meds) -Counseling/Education -Risk Reduction -Adherence -Complaints -Fears -New illnesses 	<ul style="list-style-type: none"> -Creatinine* (preferable for all cases but required if to start TDF) -ALT and/or AST** (required if to start NVP) -Hgb, WBC (required if to start AZT) -CD4 -Urine protein -If available chemistry panel to include glucose, cholesterol, triglycerides 	<ul style="list-style-type: none"> -RPR (repeat yearly) -PAP smear (if unavailable, then visualization with acetic acid screening) -If available, HBsAg -Pregnancy testing in women of reproductive age
Every month for first 3 months	<ul style="list-style-type: none"> -Targeted History & Physical -Counseling/Education -Risk Reduction -Adherence -Complaints -Fears -Side effects -New illness/IRIS 	<ul style="list-style-type: none"> -If on AZT- Hgb -If on NVP- ALT and/or AST 	
At 3 month visit	As above	<ul style="list-style-type: none"> -If on AZT- Hgb -If on NVP- ALT -If on TDF Creatinine* viral load if available 	
Every 6 months	<ul style="list-style-type: none"> -Targeted History & Physical -Counseling/Education -Risk Reduction -Adherence -Complaints -Side effects -Fears -New Illness 	<ul style="list-style-type: none"> -If on TDF- Creatinine* -WBC, Hgb, ALT CD4 -viral load if available -If on PI-containing regimen, consider Chemistry profile (including LFTs, glucose, cholesterol, and triglycerides) on a yearly basis if normal; if abnormal, treat as indicated 	<ul style="list-style-type: none"> -Repeat PAP at 6 months and if normal, every 12 months -If visual screen only with acetic acid, repeat as with Pap smear if normal; if abnormal, refer for treatment

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* Calculate Creatinine Clearance (CrCl):

(For men)

$$\text{CrCl} = (140 - \text{age}) (\text{weight in kg}) / 72 \times \text{serum Creatinine (mg/dl)}$$

or

$$\text{CrCl} = (140 - \text{age}) (\text{weight in kg}) / 815 \times \text{serum Creatinine } (\mu\text{mol/l})$$

(For Women)

$$\text{CrCl} = (140 - \text{age}) (\text{weight in kg}) (0.85) / 72 \times \text{serum Creatinine (mg/dl)}$$

or

$$\text{CrCl} = (140 - \text{age}) (\text{weight in kg}) (0.85) / 815 \times \text{serum Creatinine } (\mu\text{mol/l})$$

** If unable to perform Creatinine, ALT, or other essential laboratories then specimen should be sent to nearest facility where test can be performed.

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**ANTIRETROVIRAL THERAPY FOR
INDIVIDUALS WITH TUBERCULOSIS CO-INFECTION**

Scenario 1: Newly diagnosed TB (category I) and HIV co-infection		Recommended ART Regimens
No CD4 count facility (patient clinically stable and no history of any other stage 2 or 3 conditions).	<ul style="list-style-type: none"> Start category I TB treatment immediately Reassess monthly and consider initiation of ART if clinical condition of patient deteriorates while on TB treatment or refer patient to higher level of care If patients condition stable consider ART after TB treatment 	<ul style="list-style-type: none"> If patient stable and completes TB treatment follow normal criteria for initiating ART where there is no CD4 count available
No CD4 count facility (patient seriously ill or with history of other stage 3 or 4 conditions)	<ul style="list-style-type: none"> Start category I TB treatment immediately Start ART as soon as TB medications are tolerated (usually within 2-3 weeks) 	<ul style="list-style-type: none"> Use TDF/FTC + EFV If patient has anemia (<10g/dl) treat anemia and use TDF+ 3TC+ EFV (preferred) or ABC + 3TC + EFV (alternative)
CD4 count available (>350/mm ³)	<ul style="list-style-type: none"> Start category I TB treatment immediately Reassess as per TB review schedule and consider initiation of ART if clinical condition of patient deteriorates while on TB treatment or refer patient to higher level of care If patients condition stable consider ART after TB treatment 	<ul style="list-style-type: none"> If patient stable and completes TB treatment follow normal criteria for initiating ART where there is CD4 count available
CD4 count available (200-350/mm ³)	<ul style="list-style-type: none"> Start category I TB treatment immediately Reassess monthly and consider initiation of ART if clinical condition of patient deteriorates while on TB treatment or refer patient to higher level of care If patients condition stable consider ART after category I TB treatment 	<ul style="list-style-type: none"> If patient stable and completes TB treatment follow normal criteria for initiating ART where there is CD4 count available
CD4 count available (50-200/mm ³)	<ul style="list-style-type: none"> Start category I TB treatment immediately Start ART as soon as TB medications are tolerated (usually within 2-3 weeks) or at the end of intensive phase of TB treatment 	<ul style="list-style-type: none"> Use TDF/FTC + EFV If patient has anemia (<10g/dl) treat anemia and use TDF+ 3TC+ EFV (preferred) or ABC + 3TC + EFV (alternative)
CD4 count available (<50/mm ³)	<ul style="list-style-type: none"> Start category I TB treatment immediately Start ART as soon as TB medications are tolerated (usually within 2-3 weeks) 	<ul style="list-style-type: none"> Use TDF/FTC + EFV If patient has anemia (<10g/dl) treat anemia and use TDF+ 3TC+ EFV (preferred) or ABC + 3TC + EFV (alternative)

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Scenario 2: Newly diagnosed TB (category II) and HIV co-infection		Recommended ART Regimens
	<ul style="list-style-type: none"> Evaluate eligibility for ART as in scenario 1 above Commence category II TB treatment Choice of ART regimen should take into account that patients would be on rifampicin throughout TB treatment 	<ul style="list-style-type: none"> Use TDF/FTC + EFV If patient has anemia (<10g/dl) treat anemia and use TDF+ 3TC+ EFV (preferred) or ABC + 3TC + EFV (alternative)

Scenario 3: PLHIV on ART who develops TB		Recommended ART Regimens
Develops TB while on ART	<ul style="list-style-type: none"> Start TB treatment immediately and if ART regimen includes nevirapine, substitute nevirapine with efavirenz and continue ART OR refer the patient for TB treatment if TB service is situated in another facility 	<ul style="list-style-type: none"> Refer OR Evaluate for clinical failure and consider for second line ART IN consultation with HIV specialist

Scenario 4: Patient on TB treatment is diagnosed HIV positive		Recommended ART Regimens
HIV diagnosed during intensive phase of category I or II TB treatment	<ul style="list-style-type: none"> Refer to instructions in scenario 1 and 2 above. 	
HIV diagnosed during the continuation phase of TB treatment	<ul style="list-style-type: none"> If patient is clinically stable consider initiating ART after completion of TB treatment. If patient has other evidence of stage 3 or 4 condition refer to instructions in scenario 1 and 2 above. If ART is required immediately avoid nevirapine in patients on category II TB treatment or category I with abnormal liver function 	

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Scenario 5: HIV and TB treatment in pregnancy		Recommended ART Regimens
<p>HIV pregnant woman on ART develops TB</p>	<ul style="list-style-type: none"> • Reassess ART regimen in view of potential drug-drug interaction with anti-tuberculosis drugs or clinical failure • Thereafter commence anti-tuberculosis treatment 	<ul style="list-style-type: none"> • Consider either: Changing NVP to EFV if after 1st trimester; switching to AZT/3TC/ABC • OR Evaluate for clinical failure and consider for second line ART in consultation with HIV specialist
<p>Pregnant woman on TB treatment tested positive for HIV</p>	<ul style="list-style-type: none"> • Continue TB treatment • Refer for PMTCT or ART clinic to determine eligibility and choice of ARV regimen • Where possible defer ART until end of TB treatment or in the second trimester of pregnancy 	<ul style="list-style-type: none"> • If completed TB or in second trimester of pregnancy use AZT+ 3TC + NVP • Can use EFV after 1st trimester of pregnancy- preferred if on rifampicin

ADVERSE EFFECTS AND TOXICITY

Goals of Managing Drug Adverse Effects

- Maintain good adherence
- Reduce the potential adverse impacts of drug side effects
- Identify serious adverse drug reactions and manage appropriately

Principles in Managing Toxicities

- Determine the seriousness of the toxicity and manage according to severity
- Establish whether the adverse event is due to ART, some other medication or illness (e.g., viral hepatitis, malaria, IRIS)
- When changing a regimen due to toxicity, never stop only one ARV drug (the patient should always be on three-four); however, an individual drug may be switched due to intolerance
- Stress adherence despite mild to moderate reactions
- If there is a need to stop ART because of severe life-threatening toxicity, stop all the drugs together until the patient is stabilized
- Adverse events should be recorded and reported regularly to the HIV/AIDS program manager and to the National Pharmacovigilance Unit at the Pharmacy Regulatory Authority
- Early complications are seen most commonly when therapy is started in pts with severe immunodeficiency. Mortality is increased in 1st 6 months on treatment, especially in patients with Stage IV disease and severe immunosuppression

General Prevention and Management of Adverse Effects

- Educate patient about possible adverse effects
- Consider other medical conditions (e.g. hepatitis) and medications when selecting a regimen to decrease risk
- Follow recommendations for laboratory and clinical monitoring while on ARVs
- Educate about danger signs of life-threatening conditions
- Make sure the patient knows how to reach their provider when they have questions or concerns

WHO TOXICITY ESTIMATES

Grade 1 (mild):

- Transient or mild discomfort, no limitation in activity no medical intervention needed
- ◆ Does not require change in therapy, symptomatic treatment may be given

Grade 2 (moderate):

- Limitation in activity, some assistance may be needed; no or minimal medical intervention/therapy required
- ◆ Continue ART if possible; if no improvement consider substitution with a drug in the same ARV class but with a different toxicity profile

Grade 3 (severe):

- Marked limitation in activity, some assistance usually required, medical intervention required, possible hospitalization
- ◆ Substitute the offending drug without stopping therapy

Grade 4 (severe life-threatening):

- Extreme limitation in activity, significant assistance required, significant medical intervention/therapy required, hospitalization or hospice care
- ◆ Discontinue all ARV drugs, manage the medical event until patient is stable and toxicity has resolved

IMMUNE RECONSTITUTION INFLAMMATORY SYNDROME

Immune Reconstitution Inflammatory Syndrome (IRIS) is an exaggerated inflammatory reaction from a re-invigorated immune system presenting as “unmasking” of previously sub-clinical opportunistic infections OR clinical deterioration of pre-existing opportunistic infections OR development of autoimmune disease

- Onset: usually within 2-12 weeks after starting ART
- Frequency: 10% among all pts on ART, up to 25% when ART initiated with CD4<50 cells/mm³
- Risk factors:
 - Initiating ART close to diagnosis of an opportunistic infection
 - Initiating ART when CD4 is less than 50 cells/mm³
 - Rapid initial fall in HIV-1 RNA level in response to ART in patients with low CD4 counts
- Most commonly seen with TB, cryptococcal disease and Mycobacterium avium complex infection

Management of IRIS

- Have high index of suspicion with early complications
- ART should be continued
 - If ART continuation is impossible, temporarily interrupt ART and restart same regimen after OI or inflammatory condition is treated
- Treat OI or inflammatory condition
- Corticosteroid treatment in moderate to severe cases: Prednisolone or Prednisone 0.5 mg/kg/day for 5-10 days

CHANGING/ STOPPING ART

Goals in Changing Regimens

- Restore patients clinical, immunologic and virologic response when treatment failure occurs
- Manage serious toxicities and intolerance
- Reduce likelihood of adverse events when certain medical conditions occur (e.g., pregnancy, TB)

Indications for Changing Treatment

ART may be changed because

- Intolerance or unresolved and prolonged side effects
- Failure- clinical, immunologic, or virologic as outlined above
- Toxicity such as anemia, peripheral neuropathy, liver or renal abnormalities
- Poor adherence- change indicated only to simplify dosing schedule to improve adherence
- Occurrence of active TB: (refer to TB/HIV co infection)
- Occurrence of pregnancy: if regimen contains EFV
- New therapies: may consider change in regimen as new agents become available with better efficacy and/or lower toxicity

Before changing therapy in treatment failure, need to rule out

- Immune Reconstitution Inflammatory Syndrome (IRIS)
- Untreated inter-current OIs
- Poor adherence: MUST be corrected and therapy change only after adherence issues have been addressed;
- Inadequate dosing
- Drug-drug interactions resulting in reduced ART blood levels (e.g. NVP + Rifampin)
- Poor absorption of drugs due to adverse effects (e.g., nausea/vomiting)
- Inter-current infections causing transient decrease in CD4 count (if possible, repeat CD4 to confirm immunologic failure)

CHANGING ART DUE TO TOXICITIES

ARV Drug	Common Associated Toxicity	Suggested Substitute
ABC	Hypersensitive reaction	AZT or TDF or d4T
AZT	Severe anemia ¹ or neutropenia ² Severe gastrointestinal intolerance ³	TDF or d4t or ABC
	Lactic acidosis	TDF or ABC ⁴
d4T	Lactic acidosis Lipoatrophy / metabolic syndrome ⁵	TDF or ABC
	Peripheral neuropathy	AZT or TDF or ABC
TDF	Renal toxicity (renal tubular dysfunction)	AZT or ABC or d4T
EFV	Persistent and severe central nervous system toxicity ⁶	NVP or TDF or ABC (or any PI ⁸)
	Potential teratogenicity (first trimester of pregnancy or woman not using adequate contraception)	NVP or ABC (or any PI ⁸)
NVP	Hepatitis	EFV or TDF or ABC (or any PI ⁸)
	Hypersensitive reaction	TDF or ABC (or any PI ⁸)
	Severe or life threatening rash (Stevens –Johnson syndrome) ⁷	

¹ Exclude malaria in areas of stable malaria; severe anemia (grade 4) is defined as Hb <6.5 g/dl

² Defined as neutrophil cell count <500/mm³ (grade 4)

³ Defined as severe, refractory gastrointestinal intolerance that prevents ingestion of ARV drug regimen (e.g. persistent nausea and vomiting)

⁴ Re-initiation of ART should not include d4T or AZT in this situation. TDF or ABC is preferred

⁵ Substitution of d4T may not reverse lipoatrophy

⁶ e.g. persistent hallucinations or psychosis

⁷ Severe rash is defined as extensive rash with desquamation, angioedema, or a reaction resembling serum sickness; or a rash with constitutional findings such as fever, oral lesions, blistering, facial oedema or conjunctivitis; Stevens-Johnson syndrome can be life-threatening. For life-threatening rash, substitution with EFV is not recommended, although this approach has been reported in a small number of patients in Thailand without recurrence of rash.

⁸ PI class should be preferentially reserved for second-line therapy as no potent regimens have been identified for recommendation following initial PI failure

CHANGING ART DUE TO TREATMENT FAILURE

Treatment failure is defined by the following criteria:

Clinical Failure

- Clinical disease progression signaled by new or recurrent WHO Stage 3 or 4 condition when ART has been given sufficient time to induce a protective degree of immune restoration (after 6 months). Often associated with weight loss and drop in hemoglobin
- NOTE: Must exclude immune reconstitution inflammatory syndrome (IRIS). See above. Immune reconstitution inflammatory syndrome is not an indication for changing ART
- Time sequence of events in treatment failure: Virologic failure occurs first followed by immunologic and then clinical failure

Immunologic failure

- A fall in the CD4 counts 50% from the peak value on treatment OR a decline to pre-therapy baseline or below OR persistent CD4 levels below 50 cells/mm³ after 12 months on therapy.
- If CD4 increase is less than 50 at 6 months review patient and consider treatment failure
- When ART is started with very advanced disease it may take longer to see clinical or immunologic improvement and in some cases patients may never achieve substantial increase in CD4

Virologic failure

- Where Viral load is available, the following may suggest failure
 - Plasma HIV viral load > 400 copies/ml after 6 months on therapy
 - NOTE: Blips- defined as single levels of 50-1000 c/mL, are not considered failure, repeat viral load should be performed as soon as possible
 - In patients who appear to be failing treatment and the VL is undetectable consider undiagnosed opportunistic infections or other concomitant illnesses

Factors Leading to Treatment Failure

- Poor adherence to treatment
- Prior exposure to antiretroviral treatment with development of resistance
- Primary viral resistance (infected with resistant HIV strain)
- Inadequate drug absorption
- Suboptimal dosing (e.g., sharing drugs, cutting dose because of side effects)
- Inadequate or inconsistent drug supply

INDICATIONS FOR CONSULTATION WITH OR REFERRAL TO AN HIV SPECIALIST

- Before initiating or changing ART in
 - Pregnant women or women at risk for pregnancy with CD4 counts 250-350 cells/mm³
 - Patients co-infected with viral hepatitis
 - Patients with ALT/AST >5-fold the upper limits of normal range
- Co-infection with TB if on non-EFV regimen
- Failure or inability to tolerate second-line therapy or when on other PI-based regimen
- Severe or life-threatening adverse reactions
- Before restarting ART after severe or life-threatening adverse reactions
- Inability to tolerate therapy despite change in regimen
- Patient is asymptomatic with no CD4 count available or with CD4>200 and patient wishes to start ART

STOPPING ARV THERAPY

Considerations in stopping therapy

- Patient's inability to tolerate all available ARV medications
- Patient's request to stop, after appropriate counseling
- Occurrence of treatment failure after exhausting all ART regimens and OI treatment options and in terminal condition

Treatment Failure with No Further Treatment Options

- Continue the failing ART regimen unless toxicities or drug interactions make the clinical situation worse for the patient
- Even with treatment failure the regimen is likely to have some residual antiviral activity
- Stopping therapy in the setting of virologic failure can be associated with rapid falls in CD4 counts and development of opportunistic complications

Temporary Discontinuation of ARV Therapy

- May be needed because of serious drug toxicity, intervening illness or surgery that precludes oral intake, or ARV non-availability
- Stop **ALL** the drugs when discontinuing therapy
 - NNRTI drugs (EFV, NVP) have longer half-lives and may be detected at significant levels up to 3 wks after the last dose; If all components of an NNRTI-based regimen are stopped at the same time, the patient will essentially be on monotherapy for a period of time and at increased risk for resistance
 - Consider discontinuing EFV or NVP and continue the NRTIs for 1 additional week, if feasible

POST EXPOSURE PROPHYLAXIS

Risk of Acquiring HIV after Occupational Exposure

- Risk of acquiring HIV infection following occupational exposure to HIV infected blood is low
- Average risk for HIV transmission after percutaneous exposure to HIV infected blood in healthcare settings is approx 1 per 300
- After mucocutaneous exposure < 1 in 1000
- No risk of transmission where intact skin is exposed to HIV infected blood

Factors associated with an increased risk of occupationally acquired HIV infection

- Deep injury
- Visible blood on the device which caused the injury
- Injury with a needle from artery or vein
- Terminal HIV illness in source patient

Body fluids and materials which may pose a risk of HIV transmission

- Amniotic fluid
- Cerebrospinal fluid
- Human breast milk
- Pericardial fluid
- Peritoneal fluid
- Pleural fluid
- Saliva in association with dentistry
- Synovial fluid
- Unfixed human tissues and organs
- Vaginal secretions
- Semen
- Any other fluid if visibly bloodstained
- Fluid from burns or skin lesions

MANAGEMENT OF OCCUPATIONAL EXPOSURES TO INFECTIOUS SUBSTANCES

Immediately after Exposure

1) Clean the Exposure Site

- If a skin wound, wash with soap and running water. If the exposed area is an eye or mucous membrane, flush with copious amounts of clean water
- DO NOT USE BLEACH or other caustic agents/disinfectants to clean the exposure site

2) Contact your On Site In-Charge/ Supervisor

- HIV/ ARV Nurse In-Charge
- Over all SIC
- Lab Manager

3) Responsibilities of the Clinical Officer or Medical Officer

- Determine if the exposure is potentially high risk based on the information in the box below
- If exposure is considered high risk: refer to closest VCT centre IMMEDIATELY and arrange for shortened version of pre-test counseling and HIV rapid test for exposed employee. If this is likely to take longer than 1 hour, give first dose of PEP before referring
- Explain that all HIV testing is CONFIDENTIAL
- Ensure the exposed employee also has a FBC and liver test (ALT) done
- Arrange post test counseling
- Counsel regarding Post Exposure Prophylaxis: risks and benefits
- Complete the Report Form describing the details surrounding the exposure
- Determine the need for post exposure prophylaxis (PEP) based on the nature of the exposure and the risks and benefits of taking (or not taking) anti-retroviral medications. **PEP should be started preferably within 1–2 hours of the exposure.** If not started within 72 hours of the exposure, PEP will not be provided, as it is not likely to be effective after this time period.

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NOTE:

PEP SHOULD NOT BE GIVEN TO EXPOSED EMPLOYEES WHO REFUSE HIV TESTING OR WHO TEST POSITIVE AT THE INITIAL TEST

IF AN EMPLOYEE DOES TEST POSITIVE INITIALLY, REFER TO ARV CLINIC FOR ASSESSMENT OF TREATMENT ELIGIBILITY AFTER ADEQUATE COUNSELING (OBSERVE CONFIDENTIALITY!!!)

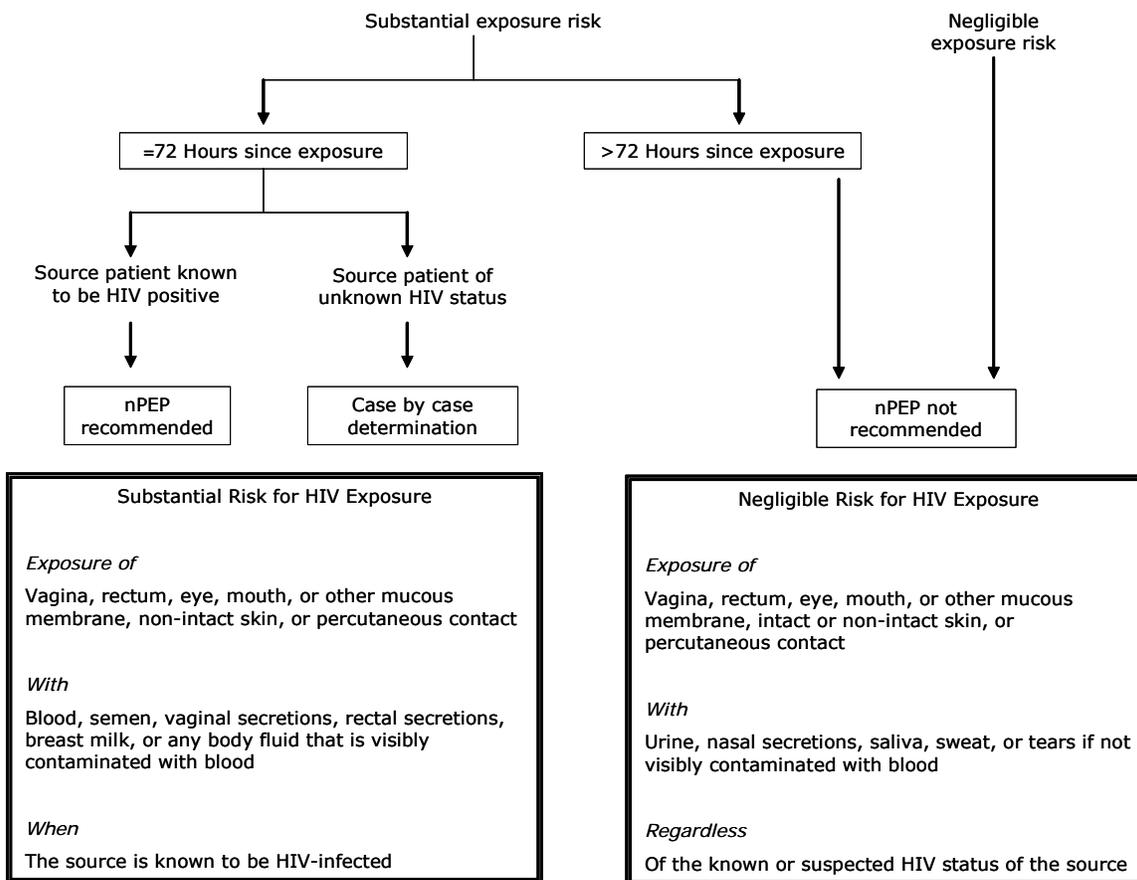
RECOMMENDED PROPHYLAXIS

No evidence indicates that any specific antiretroviral medication or combination of medications is optimal for use as PEP. However, on the basis of the degree of experience with individual agents in the treatment of HIV-infected persons, certain agents and combinations are preferred.

Risk Category	ART	Duration
No risk: intact skin	Not recommended	
Medium risk: Invasive injury, No blood visible on needle, High risk: Large volume of blood/ fluid, Known HIV infected patient, hollow bore needle, deep extensive injury	AZT 300 mg PO 12hrly 3TC 150 mg PO 12hrly plus LPV/r*	28 days
*For patients with hemoglobin less the 10gm/dl replace AZT/3TC with TDF/FTC		

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MANAGEMENT OF NON-OCCUPATIONAL EXPOSURE

Algorithm for evaluation and treatment of possible non occupational HIV exposures



Ref MMWR Jan 21, 2005
(nPEP = non occupational exposure PEP)

Follow-Up of Exposed Persons:

- An HIV blood test on the day of the exposure; this test needs to be repeated at 6 weeks, 3 months and 6 months post exposure
- An HIV blood test if client experiences an acute illness that includes fever, rash, myalgia, fatigue, malaise, and lymphadenopathy
- Evaluation by a physician within 72 hours after starting PEP and monitoring for side effects for at least 2 weeks

COTRIMOXAZOLE PROPHYLAXIS AGAINST OPPORTUNISTIC INFECTIONS

RECOMMENDATIONS FOR COTRIMOXAZOLE IN INFANTS AND CHILDREN

Initiating COTRIMOXAZOLE (CTX) prophylaxis in infants and children

- Begin CTX prophylaxis at 6 wks in all HIV-exposed infants and continue until HIV infection excluded
- Children with presumptive diagnosis of PCP or other symptomatic HIV disease should be treated and CTX prophylaxis continued until HIV infection has been definitively excluded
- Infants with documented HIV infection
 - Less than 1 yr: give CTX regardless of symptoms or CD4%
 - More than 1 yr: give CTX if Stage 2,3, or 4 HIV or if CD4% <25%
 - CTX prophylaxis will be offered to all children living with HIV, regardless of clinical stage or CD4%
- Children with history of treated PCP should be administered secondary CTX prophylaxis with same regimen used for primary prophylaxis

Discontinuation of CTX prophylaxis in infants and children

- CTX prophylaxis can be discontinued when HIV infection has been definitively excluded
- Primary CTX prophylaxis should be continued in HIV-infected children irrespective of immune recovery due to antiretroviral therapy because of their continued increased risk of bacterial infections; in children >5 yrs on ART with good immune recovery clinically and with CD4 count and secure supply of drugs, discontinuation of CTX prophylaxis can be considered in accordance with adult/adolescent guidelines
- Secondary CTX prophylaxis should be continued in HIV-infected children irrespective of immune recovery due to antiretroviral therapy because of their continued increased risk of bacterial infections; in children >5 yrs on ART with good immune recovery clinically and with CD4 count and secure supply of drugs, discontinuation of CTX prophylaxis can be considered in accordance with adult/adolescent guidelines
- CTX should be restarted if the CD4% falls below the age-specific threshold for initiation or with new or recurrent WHO clinical Stage 2,3,4 condition
- Children with history of severe adverse reactions to CTX or other sulfa drugs should not be prescribed CTX: dapsone 2 mg/kg is an alternative and the same guidelines apply

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- o CTX may need to be discontinued if serious adverse events occur that may be due to CTX (extensive exfoliative rash, Stevens-Johnson syndrome, severe anemia or pancytopenia)

CTX PROPHYLAXIS IN CHILDREN

RECOMMENDATIONS			
Situation	Age	When to Start	When to Stop
<p>HIV Exposed Infant</p> <p>(Defined as a child born to an HIV infected mother or breastfeeding from an HIV infected mother, until infection can be excluded.)</p>	6 weeks of age (at first postnatal visit or when first recognized)	Initiate Cotrimoxazole prophylaxis in ALL infants born to an HIV infected mother irrespective of any ARVs received during pregnancy and/or labor.	Discontinue Cotrimoxazole prophylaxis after exclusion of HIV infection at least 6 weeks after complete cessation of breastfeeding (PCR is negative or antibody test is negative,)
<p>HIV Infected Infant</p> <p>(Including all infants identified as HIV infected during the first year of life by PCR or clinical diagnosis of HIV infection with a positive antibody test.)</p>	<12 months	Cotrimoxazole prophylaxis is indicated regardless of CD4 percentage or clinical status or WHO stage	<p>Children < 5 years: Maintain on Cotrimoxazole prophylaxis until age 5 years irrespective of clinical and immunologic response</p> <p>Children > 5 years: can be reassessed and consideration to discontinue Cotrimoxazole prophylaxis should be in accordance with the recommendations for adults and adolescents</p>
	≥12 months to 4 years	WHO clinical stages 2, 3 and 4 regardless of CD4 percentage OR any WHO stage and CD4 <25%	
	≥5 years	Follow adult recommendations	
<p>Presumptive Symptomatic HIV Disease</p>	<18 months	Start (or continue) CTX prophylaxis regardless of CD4.	
<p>Any Child with a history of PCP</p>	All ages	Administer secondary prophylaxis.	

See Annex 3 for Cotrimoxazole formulations and dosage for infants and children living with HIV or exposed to HIV

RECOMMENDATIONS FOR COTRIMOXAZOLE PROPHYLAXIS IN ADULTS AND ADOLESCENTS

Adults with history of severe adverse reactions -Grade 4 (see *WHO toxicity Estimates* table above) to CTX or other sulfa drugs should not be prescribed CTX: dapsons 100 mg/day is an alternative and same guidelines apply.

- Because dapsons is less effective than CTX in preventing PCP and does not have as broad antibacterial spectrum, may attempt desensitization to CTX, but only if previous non-serious adverse reaction (Grade 1 and 2 only)

Protocol for cotrimoxazole desensitization among adults and adolescents

STEP	DOSE
Day 1	80 mg sulfamethoxazole + 16 mg trimethoprim (2 ml of oral suspension ¹)
Day 2	160 mg sulfamethoxazole + 32 mg trimethoprim (4 ml of oral suspension ¹)
Day 3	240 mg sulfamethoxazole + 48 mg trimethoprim (6 ml of oral suspension ¹)
Day 4	320 mg sulfamethoxazole + 64 mg trimethoprim (8 ml of oral suspension ¹)
Day 5	One single-strength sulfamethoxazole-trimethoprim tablet (400 mg sulfamethoxazole + 80 mg trimethoprim)
Day 6 - Onwards	Two single-strength sulfamethoxazole-trimethoprim tablets or one double strength tablet (800 mg sulfamethoxazole + 160 mg trimethoprim)
¹ Cotrimoxazole oral suspension is 40 mg trimethoprim + 200 mg sulfamethoxazole per 5 ml	

Initiation of primary prophylaxis

- Initiate for patients with WHO Stage 3 or 4 disease, regardless of CD4 count; if CD4 available, initiate if CD4<350, regardless of clinical stage. If WHO Stage 2 and no CD4 count, initiate CTX
 - Dose: 960 mg daily (800mg sulfamethoxazole + 160mg trimethoprim)
 - Pregnant women: CTX can be safely continued or initiated during pregnancy regardless of stage of pregnancy.
 - women living in malaria zones who are on CTX prophylaxis, no need for additional IPT for malaria (fansidar)
 - CTX can be continued during breastfeeding

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- Secondary prophylaxis: patients with history of treated PCP should be treated with CTX prophylaxis in same regimen as for primary prophylaxis

Discontinuation of primary prophylaxis

- Stop CTX if there is immune recovery whilst on antiretroviral therapy - CD4 is above 350 for at least six (6) months (based on initiation due to effect in decreasing morbidity and mortality, and incidence of malaria and bacterial infections)
- Stop CTX if patient develops Adverse Drug Reaction or Drug Toxicity such as: Jaundice, Severe Anaemia or pancytopenia or Rash (extensive exfoliative dermatitis, Stevens-Johnson syndrome)
- In absence of CD4 monitoring, no consensus but can consider discontinuation of CTX in patient on ART for more than 1 yr who has no Stage 2,3,4 events, good adherence and secure ARVs supply
- If CTX discontinued, should be restarted if the CD4 falls below the threshold for initiation or with new or recurrent WHO clinical Stage 2,3,4 condition
- Discontinuing secondary prophylaxis: same as for primary prophylaxis
- CTX Adverse effects
 - Monitor potential side effects of CTX clinically every 3 months and manage accordingly (see Table below); no specific lab monitoring required, but lab evaluation may be indicated depending on signs and symptoms. Most common side effects: bone marrow suppression, skin rash, hepatotoxicity

COTRIMOXAZOLE TOXICITY GRADING SCALE FOR ADULTS AND ADOLESCENTS

TOXICITY	CLINICAL DESCRIPTION	RECOMMENDATION
Grade 1	Erythema	Continue Cotrimoxazole prophylaxis with careful and repeated observation and follow up Provide symptomatic treatment, such as antihistamines, if available
Grade 2	Diffuse maculopapular rash, dry desquamation	Continue Cotrimoxazole prophylaxis with careful and repeated observation and follow up Provide symptomatic treatment, such as antihistamines, if available
Grade 3	Vesiculation, mucosal ulceration	Cotrimoxazole should be discontinued until the adverse effect has completely resolved (usually two weeks), and then reintroduction or desensitization can be considered
Grade 4	Exfoliative dermatitis, Stevens-Johnson syndrome or erythema multiforme, moist desquamation	Cotrimoxazole should be permanently discontinued

- Timing of CTX prophylaxis in relation to initiation of ART: start CTX first and initiate ART two weeks later if no adverse effects from CTX
- Treatment of bacterial infections, malaria and PCP/Toxoplasmosis in patients on CTX prophylaxis:
 - Use alternative antibiotic for bacterial infections and continue CTX prophylaxis
 - PCP/Toxo: stop CTX prophylaxis and treat infection, then restart prophylaxis after treatment course
 - Malaria: treat with agent that does not include sulfadoxine-pyrimethamine, if possible

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CTX PROPHYLAXIS IN ADULTS AND ADOLESCENTS

RECOMMENDATIONS		
Situation	When to Start	When to Stop
CD4 count is not available	WHO clinical stage 2, 3, 4	<p>Do not discontinue Cotrimoxazole prophylaxis especially if bacterial infections and malaria are common HIV-related conditions</p> <p>BUT</p> <p>Stop if patient develops Adverse Drug Reaction or Drug Toxicity such as: <i>Jaundice, Severe Anaemia or pancytopenia or Rash (extensive exfoliative dermatitis, Stevens-Johnson syndrome)</i></p>
CD4 count is available	CD4 < 350, in any WHO clinical stage	<p>Stop Cotrimoxazole prophylaxis if there is immune recovery whilst on antiretroviral therapy - CD4 is above 350 for at least six (6) months</p> <p>OR</p> <p>IF patient develops Adverse Drug Reaction or Drug Toxicity such as: <i>Jaundice, Severe Anaemia or Pancytopenia or Rash (extensive exfoliative dermatitis, Stevens-Johnson syndrome)</i></p>

ANNEX 1. WHO STAGING ADULTS AND ADOLESCENTS

WHO CLINICAL STAGING (2006) OF HIV DISEASE IN ADULTS AND ADOLESCENTS

CLINICAL STAGE 1

- Asymptomatic
- Persistent generalized lymphadenopathy

CLINICAL STAGE 2

- Moderate unexplained¹ weight loss (under 10% of presumed or measured body weight)²
- Recurrent respiratory tract infections (sinusitis, tonsillitis, otitis media, pharyngitis)
- Herpes zoster
- Angular cheilitis
- Recurrent oral ulceration
- Papular pruritic eruptions
- Seborrhoeic dermatitis
- Fungal nail infections

CLINICAL STAGE 3

- Unexplained¹ severe weight loss (over 10% of presumed or measured body weight)²
- Unexplained¹ chronic Candidia for longer than one month
- Unexplained¹ persistent fever (intermittent or constant for longer than one month)
- Persistent oral Candidiasis
- Oral hairy leukoplakia
- Pulmonary tuberculosis
- Severe bacterial infections (e.g. pneumonia, empyema, pyomyositis, bone or joint infection, meningitis, bacteraemia)
- Acute necrotizing ulcerative stomatitis, gingivitis or periodontitis
- Unexplained¹ anaemia (below 8 g/dl), neutropenia (below 0.5 x 10⁹/l) and/or chronic thrombocytopenia (below 50 x 10⁹ /l)

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CLINICAL STAGE 4³

- HIV wasting syndrome
- Pneumocystis pneumonia
- Recurrent severe bacterial pneumonia
- Chronic herpes simplex infection (orolabial, genital or anorectal of more than one month's duration or visceral at any site)
- Oesophageal candidiasis (or candidiasis of trachea, bronchi or lungs)
- Extrapulmonary tuberculosis
- Kaposi sarcoma
- Cytomegalovirus infection (retinitis or infection of other organs)
- Central nervous system toxoplasmosis
- HIV encephalopathy
- Extrapulmonary cryptococcosis including meningitis
- Disseminated non-tuberculous mycobacteria infection
- Progressive multifocal leukoencephalopathy
- Chronic cryptosporidiosis
- Chronic isosporiasis
- Disseminated mycosis (extrapulmonary histoplasmosis, coccidiomycosis)
- Recurrent septicaemia (including non-typhoidal Salmonella)
- Lymphoma (cerebral or B cell non-Hodgkin)
- Invasive cervical carcinoma
- Atypical disseminated leishmaniasis
- Symptomatic HIV-associated nephropathy or HIV-associated cardiomyopathy

¹ Unexplained refers to where the condition is not explained by other conditions.

² Assessment of body weight among pregnant woman needs to consider the expected weight gain of pregnancy.

³ Some additional specific conditions can also be included in regional classifications, such as the reactivation of American trypanosomiasis (meningoencephalitis and/or myocarditis) in the WHO Region of the Americas and penicilliosis in Asia.

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

ANTIRETROVIRAL THERAPY FOR CHRONIC HIV INFECTION IN ADULTS AND ADOLESCENTS

ANNEX 2: Antiretroviral Dosing Guideline

Generic Drug Abbreviation Trade Name	Dosage & Food Restriction	Renal & Hepatic Insufficiency	Cautions	Frequent side effects	Serious dose related toxicity
Tenofovir TDF Viread	300 mg Q24 hours Food: none	Renal: adjust If CrCl<50 Hepatic: none	Renal insufficiency; TDF increases DDI toxicity	Nausea Vomiting Diarrhea Flatulence	Renal dysfunction follow CrCl every 6 months
Emtricitabine FTC Emtriva	200 mg Q24 hours Food: none	Renal: adjust If CrCl<50 Hepatic: none		Headache Diarrhea Nausea Rash Hyperpigmentation of palms	
TDF + FTC Truvada	1 tablet Q24 hours Food: none	As above for individual drugs	As above for individual drugs	As above for individual drugs	As above for individual drugs
Zidovudine ZDV or AZT Retrovir	300 mg Q12 hours Food: none	Renal: adjust If CrCl<10 Hepatic: none	Hemoglobin < 10 gm/dl; Contra- indicated with D4T	Headache Nausea Anorexia Vomiting Insomnia Malaise	Anemia (monitor Hgb first 12 weeks) Neutropenia Myopathy Lactic acidosis Finger nail discoloration
Lamivudine 3TC Epivir	150 mg Q12 hours or 300 mg Q24 hours Food: none	Renal: adjust If CrCl<50 Hepatic: none		Headache Nausea Diarrhea Abdominal pain Insomnia	Pancreatitis in children
AZT + 3TC Combivir	1 tablet Q12 hours Food: none	As above for individual drugs	As above for individual drugs	As above for individual drugs	As above for individual drugs
Stavudine D4T Zerit	30 mg Q12 hours (No dose increase needed after initiation)	Renal: adjust If CrCl<50 Hepatic: none	Contra- indicated with AZT/ZDV; Increased toxicity with DDI, INH, phenytoin, vincristine	Diarrhea Nausea Vomiting Headache	Peripheral neuropathy Lipoatrophy Hyperlipidemia Pancreatitis Lactic acidosis
Abacavir ABC Ziagen	300 mg Q12 hours or 600 mg Q24 hours Food: none	Renal: none Hepatic: none	Caution with alcohol	Nausea Headache Diarrhea Malaise	Hypersensitivity reaction (peaks within 2 weeks, uncommon after 12 weeks) DO NOT RECHALLENGE

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Generic Drug Abbreviation Trade Name	Dosage & Food Restriction	Renal & Hepatic Insufficiency	Cautions	Frequent side effects	Serious dose related toxicity
Didanosine DDI Videx	Initiating dose: <60kg: 125 mg Q12 hours >60kg: 200 mg Q12 hours Food: one hour before or two hours after food	Renal: adjust If CrCl<60 Hepatic: none	Reduce dose with TDF; Increased toxicity with D4T, INH, Vincristine, alcohol	Diarrhea Nausea Rash Fever Headache	Pancreatitis Peripheral neuropathy Lipoatrophy Lactic acidosis Hepatic steatosis
Nevirapine NVP Viramune	Initiating dose: 200 mg Q24 hours for 14 days; then 200mg Q12 hours Food: none	Renal: none Hepatic: avoid with moderate to severe liver disease	Hepatic failure; caution in women with CD4 count less than 250; Drug interactions: Rifampicin, ketoconazole, Birth control pills, anti- convulsants, clarithromycin; If stopping cover tail for 7 days*	Rash	Stevens Johnson Syndrome Toxic epidermal necrolysis Hepatotoxicity (monitor ALT/AST first 12 weeks) Liver failure Hypersensitivity
Efavirenz EFV Stocrin	600 mg Q24 hours Food: without food or low fat meal	Renal: none Hepatic: none	Avoid in potential pregnancy or 1 st trimester; Drug interactions: clarithromycin, warfarin, birth control pills; If stopping cover tail for 7 days*	Abnormal dreams Dizziness Insomnia Somnolence Impaired thinking Rash	Teratogenicity
Lopinavir/r LPV/r Kaletra capsules; Aluvia tablets	3 capsules Q12 hours (Kaletra) or 2 tablets Q12 hours (Aluvia) Food: with food	Renal: none Hepatic: none	Multiple drug interactions: Rifampicin, oral contraceptives, statins, anti- convulsants	Diarrhea Nausea Vomiting	Hyperlipidemia Insulin resistance Pancreatitis Transaminitis Fat redistribution

***Covering the NNRTI tail:** NNRTI (NVP and EFV) have prolonged drug concentrations after discontinuing drug. In order to decrease the likelihood of resistance, instruct patient to continue the other 2 ARV drugs after discontinuation of NNRTI for an additional 7 days.

ANNEX 3: COTRIMOXAZOLE FORMULATIONS AND DOSAGE FOR ADULTS, INFANTS AND CHILDREN LIVING WITH HIV OR EXPOSED TO HIV

Dosing

	Weight band (Kg)	Dose/day	
		Liquid 8mg/ml Suspension	Tablet SS*
Infants/Children	3.0 – 4.9	2.5 ml daily	¼ SS tab
	5.0 – 6.9	5.0 ml daily	½ SS tab
	7.0 – 9.9	7.5 ml daily	1 SS tab
	10.0–11.9	10.0 ml daily	1 SS tab
	12.0–14.9	12.5 ml daily	1 SS tab
	15.0– 16.9	15.0 ml daily	1 SS tab
	17.0 19.9	20.0 ml daily	1 SS tab
	20.0 24.9	20.0 ml daily	1 SS tab
	25.0 29.9	-	2 SS tabs
	30.0 34.9	-	2 SS tabs
	Above 35	-	2 SS tabs
Adults	1 DS tab od OR 2 SS tab od		
<p>* Single-strength (SS) tablets are trimethoprim 80 mg and sulfamethoxazole 400 mg Double-strength (DS) tablets are trimethoprim 160 mg and sulfamethoxazole 800 mg</p>			