Guidelines for the Use of Antiretroviral Therapy in HIV Positive Adults and Adolescents in Pakistan

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The National AIDS Control Program
Ministry of Health
Government of Pakistan

PREFACE:

Successful treatment of HIV/AIDS depends on strict adherence by HIV positive patients in taking their medications as instructed and for health care providers to recommend antiretroviral treatment (ART) based on rigorous scientific evidence. The devastating consequences of incorrect or partial HIV treatment are premature death, increased morbidity, development of drug resistant HIV strains, and lack of further treatment options.

The sobering lessons from other developing countries, where driven by the HIV crisis, availability of ART often preceded development of adequate health infrastructures to manage ART. The Global community sadly witnessed the tragic consequences of such ad hoc policies. The National AIDS Control Program recognizes the importance of strengthening health systems to manage and supply ART including the development of standardized treatment guidelines for HIV positive people in Pakistan. The following “Guidelines on Antiretroviral Therapy” were specifically developed in context of Pakistan through a national consultative process and incorporating strong scientific knowledge and international standards of care.

The main purpose of these guidelines is to assist health care providers in determining the optimal ART regimen for their HIV positive patients and to provide recommendations for standardized quality of care. We hope that compliance with the guidelines will reduce the risk of treatment failures, prevent ART resistance and in the long term enable Pakistan to successfully contain the HIV/AIDS epidemic.

It is crucial to for health care providers and patients to understand that treatment and care of HIV is an evolving science. While these guidelines contain the latest recommended ART practices, they are a living document. The National AIDS Control Program would like to emphasize that these guidelines will be regularly revised and updated to incorporate new information and best practices.

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Abbreviations:

AIDS	Acquired Immune Deficiency Syndrome
ANC	Antenatal clinics
ARV	Antiretroviral
ART	Antiretroviral therapy
CDC	Centers for Disease Control (USA)
CO	Community Organization
ddI	Didanosine
EFV	Efavirenz
FPC	Family planning clinics
HBV	Heptitis B virus
HCV	Hepatitis C virus
HIV	Human Immunodeficiency Virus
ID	Infectious Disease specialist
IDU	Injecting Drug Users
NACP	National AIDS Control Program
NFV	Nelfinavir
NGO	Non-governmental Organization
NVP	Nevirapine
OI	Opportunistic infection
PACP	Provincial AIDS Control Program
PEP	Post-exposure Prophylaxis
PLWHA	People Living with HIV/AIDS
PMTCT	Prevention of Mother-Child Transmission of HIV
STIs	Sexually Transmitted Infections
TB	Tuberculosis
TLC	Total Lymphocyte Count
WHO	World Health Organization
UNAIDS	United Nations Joint Co-sponsored Program on AIDS
VCT	Voluntary Counseling and Testing
3TC	Lamivudine
d4T	Stavudine
ZDV	Zidovudine

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1. Introduction

For over two decades, the HIV epidemic has spread throughout the world affecting an estimated 42 million people and killing over 20 million people since the beginning. Not a single country is now free of HIV.

Pakistan showed an increase in HIV transmission among high risk population and the recent trends are alarming. The country is now facing a concentrated epidemic in high risk populations, particularly among injecting drug users (IDUs). Survey data from IDUs in two major cities in 2004 showed that nearly 25% of them were infected with HIV/AIDS. Nonetheless at this stage the epidemic is far from generalized and there exists a window of opportunity to slow down its progression. However, the general lack of awareness and knowledge regarding HIV/AIDS, limited access to health care and antiretrovirals therapy (ART), poverty, low literacy, prevalence of risky sexual behaviors, and gender inequalities all pose a tremendous potential for the HIV epidemic to rapidly spread in Pakistan, as has been seen in other countries with similar risk factors.

According to UNAIDS and WHO forecast models the number of people living with HIV/AIDS (PLWHA) in Pakistan is estimated at 70000-80000 (0.1% prevalence). Of these 2,700 are estimated to be in need of ART (National AIDS Control Program estimates). As of December 2004, 2745 HIV infected cases, including 312 AIDS cases, were reported to the National AIDS Control Program (NACP).

The availability of highly active antiretroviral therapy (HAART) in western countries since 1996 has dramatically reduced the mortality and morbidity associated with HIV-infection and improved the quality of life of PLWHA. Although ART is not a cure and needs to be taken life-long with challenges related to adherence, side-effects and drug-resistance, HIV infection is now treatable and global efforts have made ART more affordable even in resource limited settings.

The Government of Pakistan is committed to the “3 by 5” initiative launched by the World Health Organization (WHO). This initiative targets to treat 3 million persons by 2005, which is half of the persons in need of treatment today. To reach this objective a standardized and simplified protocols, based on scientific evidence, are necessary for implementing and expanding access to ART.

2. Objectives

These guidelines aim to

- Provide a standardized and simplified approach for the use of antiretrovirals in Pakistan, based on scientific evidence and adapted to local needs and resources.
- Outline treatment strategies and recommendations for adults, including a section on children, pregnant women, special populations (IDUs, HIV-TB coinfections or Hepatitis B or C coinfections)
- Serve as a reference manual for health care professionals involved in the treatment and care of PLWHA in the public and private sector. These

guidelines are intended for physicians, nurses, psychologists, and other health care providers involved in an integrated medical care approach.

- The guidelines consider when ART should begin, which ARV regimen should be introduced, the reasons for changing ART and the regimens that should be continued if treatment has to be changed. They also address how treatment should be monitored, with specific reference to side-effects of ART and drug adherence.

3. Methods

These guidelines were developed during a national consultation workshop, from October 12th to 14th 2004, conducted by the National AIDS Control Program with the support of the World Health Organization and UNAIDS.

A panel of participants from National and Provincial AIDS Control Programs, private infectious disease specialists, public physicians identified for the HIV/AIDS treatment centers, NGOs, representatives of People Living With HIV/AIDS, UN agencies, representatives from federal and provincial levels, were invited to discuss and develop a rational consensus for the prescription and follow-up of ART in Pakistan. The participants were selected according to their experience and involvement in the field of HIV and medical care. The workshop was voluntarily limited to 20 persons.

During the workshop, international guidelines developed by WHO were reviewed as well as guidelines developed in India, and they served as reference documents for the development of these guidelines. The draft was peer-reviewed by the NACP, a panel of ID specialists, representatives of PLWHA, WHO and UNAIDS.

These guidelines will require updating at regular intervals as new scientific information and experiences becomes available.

4. Introduction to Antiretroviral therapy

A continuous high level of replication of HIV takes place from the early stages of infection. Despite this high level of replication, most patients remain well for many years and do not need ART as the infection is partially controlled by their immune system. This is the clinically latent period of HIV infection.

With time, the ongoing HIV replication leads to progressive immune system damage, in particular the destruction of lymphocytes CD4, resulting in susceptibility to opportunistic infections (OI), malignancies, HIV-related neurological diseases, wasting and ultimately death. All these syndromes define the AIDS stage of HIV infection.

Cohort studies have shown that more than 80% of the persons infected with HIV developed AIDS, 10 years after the date of infection, in absence of ART. Antiretroviral drugs aim to stop the HIV replication by blocking some viral enzymes necessary for the replication. Five classes of drugs are currently available acting on 3 distinct HIV specific targets (table 1 and figure 1). Details on formulation, doses, side effects for each of the drugs are presented in annex.

Highly active antiretroviral therapy consists of combining 3 drugs from 2 classes:

- 2 Nucleoside Reverse Transcriptase Inhibitor (NRTI) + 1 Non Nucleoside Reverse Transcriptase Inhibitor (NNRTI),

Or

- 2 Nucleoside Reverse Transcriptase Inhibitor (NRTI) + 1 Protease Inhibitor (PI).

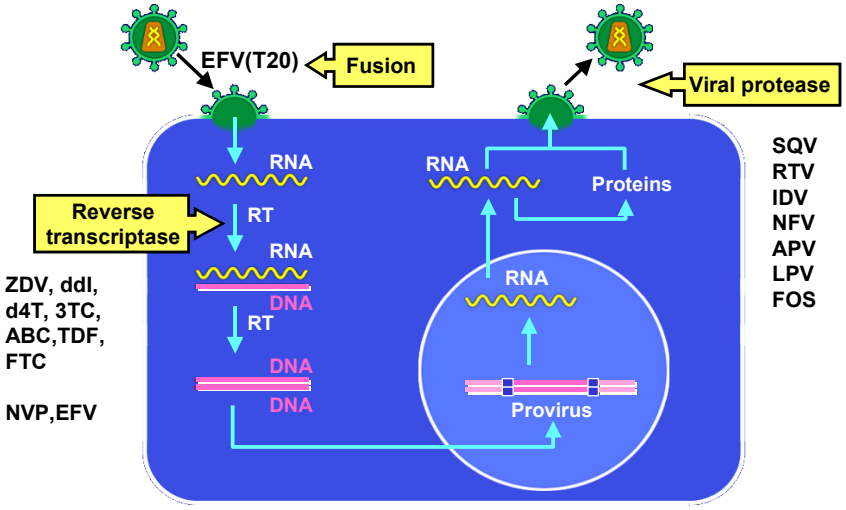
Table 1: List of Antiretroviral Drugs Approved for Clinical Use

Target	Reverse Transcriptase Enzyme			Viral protease Enzyme	Entry Inhibitor
Drug class	Nucleoside Reverse Transcriptase Inhibitor **(NRTI)**	Non Nucleoside Reverse Transcriptase Inhibitor **(NNRTI)**	Nucleotide Reverse Transcriptase Inhibitor	Protease Inhibitor **(PI)**	Fusion Inhibitor
Drugs Name	Zidovudine (ZDV or AZT)	Nevirapine (NVP)	Tenofovir (TDF)	Nelfinavir (NFV)	Enfuvirtide (T-20)
	Abacavir (ABC)	Efavirenz (EFV)		Ritonavir (RTV)	
	Didanosine (ddI	Delavirdine (DLV)-not used		Saquinavir (SQV) Lopinavir/RTV	
	Emtricitabine (FTC)			Amprenavir (APV)	
	Zalcitabine (ddC)-not used			Fosamprenavir (F-APV)	

				Atazanavir (ATZ)	

Ritonavir is generally used as a booster with other PIs for enhanced drug efficacy.

Figure 1: Current targets of antiretroviral drugs



Not all drugs can be combined together, due to potential interactions, antagonism or increased rate and severity in side effects. **The contraindicated combinations are:**

- **ZDV + D4T**
- **ddC + 3TC**
- **ddC + ddI**
- **ddC + d4T**
- **monotherapy (excepting PMTCT) or dual therapy.**

Fixed drugs combinations (FDC) combining 2 to 3 drugs in the same pill, reduces the pill-burden, simplifies the administration and favours the adherence. FDC exists for NRTI and Nevirapine, in adult dosages:

- $D4T_{30\ mg}$ /3TC $_{150\ mg}$ /Nevirapine $_{200\ mg}$,
- $D4T_{40\ mg}$ /3TC $_{150\ mg}$ /Nevirapine $_{200\ mg}$,
- ZDV $_{300\ mg}$ /3TC $_{150\ mg}$ /Nevirapine $_{200\ mg}$,
- ZDV $_{300\ mg}$ /3TC $_{150\ mg}$,
- $D4T_{30\ mg}$ /3TC $_{150\ mg}$
- $D4T_{40\ mg}$ /3TC $_{150\ mg}$

No FDC are available with Efavirenz or Protease Inhibitor drugs, except for the Lopinavir/ritonavir (LPV/r) association. Most of protease Inhibitor combination regimens have a high pill burden (10 to 15 pills a day).

Key Points:

- ART does not cure HIV infection but prolongs life, improves quality of life and reduces risk of opportunistic infections.
- To obtain maximal viral suppression is the objective goal of therapy (> 1 log)- i.e the HIV viral load becomes undetectable.
- Unlike any other infection, ART is recommended only to patients at a certain stage of the disease. The prescription of ART requires a medical evaluation to assess the medical criteria to start ART.
- Simultaneous initiation of three drugs is important. No treatment should include only 1 or 2 drugs (except for PMTCT and Post-exposure prophylaxis)
- Treatment is lifelong. Once established the treatment should not be interrupted apart from standard medical criteria. Unnecessary interruption or change, even if the patient is healthier, might expose the patient to development of a drug resistant virus compromising his/her future chance for treatment.
- ART is expensive however access to affordable treatment is slowly becoming an option.
- High level of adherence is critical. More than 95% of pills should be taken as prescribed (doses and schedule), otherwise there is a high risk of virus-resistance compromising the future chance of treatment.
- Drug-drug and food-drug interactions are common.
- The patient has a key role to play in his/her treatment and should be informed and supported for that.
- Safer sexual practices are critical even among patients on ART and showing clinical improvement.

5. Starting Antiretroviral Therapy

Entry Points

A critical point for identifying the persons in need of treatment is through access to Voluntary Counseling and Testing (VCT) services, which function as a gateway to treatment services. While there is currently a limited number of functional VCT centers, political leadership and commitment has shifted significantly in favor of establishing VCT centers and providing access to ART. Entry points must provide or facilitate the link to HIV testing and counseling. Entry points include:

Clinical services
- STI service centers/clinics
- Drug treatment centers
- Maternal Child Services (MCH)
- Hepatitis B or C services
- TB care centers/programs

Community Outreach Services:
- High risk/vulnerable populations (sex workers, injecting drug users, truck drivers)
- Men having sex with men (homosexuals, bisexuals, Hijras)
- Migrants workers (international and national)
- Blood donors,
- NGOs working with high risk or marginalized populations

Referral Services and Linkages:
- Adult and pediatric inpatient or out patient hospitals/health care facilities
- Referral systems through other public or private organizations

VCT services should include counseling regarding the options for ART treatment, in order to help the acceptance of a positive result and to inform and educate HIV infected persons to the availability of medical care services.

All clients testing HIV positive in VCT centers need to be referred to a HIV treatment center for medical examination. Two positive tests, using different tests (e.g. 2 different rapid tests, 1 rapid test+1 Elisa), are necessary to confirm HIV+ status.

An integrated family approach needs to be promoted for access to VCT and ART, with special emphasis on addressing vulnerability of women and children in accessing services. During VCT or HIV related care for men, it is part of the medical responsibility to repeatedly request the participation of the wife and children and to promote VCT and HIV care if needed for the full nuclear family.

Very few people, including health care staff, know about VCT services. A communication strategy has to be implemented to develop awareness regarding existing VCT services and future ART services among the general population and health care providers.

Criteria to Start ART

Criteria to start ART will be assessed in the ART treatment center, after referral of all HIV+ persons identified in the VCT services. Criteria to start ART should be based on standard medical criteria without any consideration of socio-economical, cultural, behavioral factors, so as to ensure an equitable access to ART to all PLWHA who need it. However, criteria/guidelines for assessing patient compliance are essential prior to initiation of ART to reduce risk of future drug resistance. Nearly 95% adherence with the treatment regimen is essential to prevent treatment failures.

Some well known risk factors for non-adherence are:

- Active alcohol or other illicit substance use
- Untreated depression
- Lack of stable home environment and family support
- Inadequate insight and understanding into the importance of compliance in treatment for HIV infection

If CD4 is not available, treatment should be initiated in all adults/adolescents presenting with clinical symptomatic disease (WHO Clinical Stages III and IV). If Total Lymphocyte Count (TLC) is available, Stage II asymptomatic disease with test values below 1,200/mm^3 should start ART. WHO clinical staging is presented in annex.

When to Start ARV in Adults/Adolescents

- **If CD4 assay *not* available:**
  - **WHO stage IV disease, *regardless* of TLC***
  - **WHO stage III disease, *regardless* of TLC**
  - **WHO stage II disease *with* TLC <1200**

  ***TLC=total lymphocyte count; only useful in symptomatic patients; in absence of CD4, would not treat stage I asymptomatic adult**
- **If CD4 assay available:**
  - **WHO stage IV disease, *regardless* of CD4**
  - **WHO stage III disease, *consider* * using CD4 <350 to assist decision-making**
  - **WHO stage I or II *if* CD4 <200**

  ***In this situation, the decision to start or defer ARV treatment should take in consideration not only the CD4 cell count and its evolution, but also concomitant clinical conditions**

If CD4 testing is available, treatment should be initiated in all patients with CD4 counts <200/mm^3 (regardless of symptoms)[1]. The treatment of patients should not be dependant on a CD4 cell count determination. However, this test can be helpful in prioritizing patients with respect to their need for immediate therapy. For example, pulmonary tuberculosis can occur at any CD4 count level, and if the CD4 cell count is well maintained ($\geq$350/mm^3), it is reasonable to defer therapy and continue to monitor the patient. CD4 might also be helpful in identifying asymptomatic patients (stage I and II) with severe immunodeficiency (<200/mm^3) who should start ART.

CD4 testing is also helpful for treatment monitoring and should be monitored every 3-6 months in patients on ART.

[1] ARV can also be considered if CD4 count is between 200 and 350/mm3 (independently of symptoms).

First line ART regimen

The suggested preferential 1st line regimen in Pakistan will be ZDV/3TC/NVP taken twice daily (BID).

- Nevirapine: For the first 14 days (2 weeks) 200mg once daily, then increase to full dose of 200mg twice daily. This dosing schedule is used to reduce the risk of side effects from NVP.
- ZDV: 300mg twice daily
- 3TC: 150 mg twice daily.

Alternative 1st line regimen is 3TC/D4T/NVP.

When using this regimen

- If patient weight is <60kg then use D4T 30mg twice daily
- If patients weight > 60kg then use D4T 40mg twice daily.

Advantages: Both regimens are well tolerated and effective, have few contraindications and are acceptable in women of child bearing age. Caution is needed when using Nevirapine in people (especially in women) when the CD4 counts are greater than 250cells/mm^3. There are no food constraint issues, 1st line regimens generally do not have any restriction or obligation, but in case of gastro-intestinal intolerance, ingesting with food can improve the symptoms, particularly with ZDV.

D4T/3TC/Nevirapine regimen is also the first line regimen in children at pediatric dosage and for pregnant women.

Fixed Drug Combinations are available (not currently in Pakistan):

- ($D4T_{30\ mg}$ /$3TC_{\ 150\ mg}$ /$Nevirapine_{\ 200\ mg}$),
- ($D4T_{40\ mg}$ /$3TC_{\ 150\ mg}$ /$Nevirapine_{\ 200mg}$).

Other formulations should also be available in order to permit the NVP lead in dose schedule in the first 2 weeks of treatment:

- ($D4T_{30\ mg}$ /$3TC_{\ 150\ mg}$) in FDC
- ($D4T_{40\ mg}$ /$3TC_{\ 150\ mg}$) in FDC
- and $Nevirapine_{200mg}$

D4T based formulation should be available in 30 mg (< 60 kg) and 40 mg (> 60 kg).

Alternative 1st line regimens in case of toxicity or contraindication are:

- D4T + 3TC + Efavirenz
- ZDV + 3TC + Efavirenz.

Table 2: Description of ARV first line drugs

1st line drugs	dose	Special consideration	use in pregnant women	use with TB drugs	Contraindications	Adverse effects	1st line substitution
D4T (preferential)	< 60kg: 30 mg bd > 60 kg: 40 mg bd	With or without food	Yes	Yes	Neuropathy Pancreatitis	Pancreatitis Peripheral neuropathy Lipoatrophy Lactic acidosis with hepatic steatosis (rare) The risk of intolerance is higher in association with ddI	ZDV
3TC * (preferential)	150 mg bd	With or without food	Yes	Yes	None	Well tolerated Lactic acidosis with hepatic steatosis (rare)	
Nevirapine (preferential)	14 first days: 200mg od then: 200mg bd	With or without food	Yes	Caution in Rifampicin based regimen	Clinical hepatitis Drug interaction with rifampicin **	Skin rash, Lyell, Stevens Johnson syndrome, Hepatic toxicity, elevated transaminase levels, life-threatening hepatitis	Efavirenz
ZDV (preferential)	300 mg bd	With or without food	Yes	Yes	Severe anemia <8 g/dl Neutropenia <750/mm^3	Anaemia, neutropenia, gastrointestinal intolerance headache, insomnia, myopathy Lactic acidosis with hepatic steatosis (rare)	D4T
Efavirenz (substitution)	600 mg od	Bed time to avoid CNS symptoms With or without food Contraceptive method	No (1st trimester)	Yes	1st trimester of pregnancy	CNS symptoms: dizziness, somnolence, insomia, confusion, hallucinations, agitation Elevated transaminase levels Skin rash	Nevirapine

* 3TC is also active on hepatitis B

** During TB treatment with rifampicin, Nevirapine can be used as an alternative drug, if EFV is contraindicated or not available, but with caution and close clinical monitoring of hepatitis symptoms.

Initial Evaluation

Medical examination

Prior to starting therapy, patients should have a confirmed positive HIV test results (by 2 different tests) and a complete history and physical examination. A detailed clinical evaluation is essential to:

- assess the clinical stage of HIV infection (based on current and past HIV-related illnesses)
- identify current illnesses that would require treatment,
- identify co-existing medical conditions (TB, Hepatitis B or C, pregnancy, major psychiatric illness) that may influence the choice of therapy,
- detail of concomitant medications including traditional therapy,
- weight,
- assess patients' readiness for therapy.

If ZDV/3TC/NVP is used as the 1st line regimen, hemoglobin to evaluate for anemia should be included in the baseline.

When D4T/3TC/NVP is used no lab test is essential to initiate the treatment unless there is a history of hepatitis B or C (or other liver disease)

If EFV is initiated in women of child bearing age and a contraceptive is not used, a pregnancy test is mandatory before start and effective contraception methods should be initiated.

Laboratory testing is not mandatory (except for the ones mentioned) prior to starting ART. However if available, Table 3 lists the laboratory test that are desirable before starting ART. Those tests should be performed if it is not a financial obstacle for the patients in accessing ART and/or if the tests are preferably free of charge.

Table 3: list of laboratory and other investigations before starting ART

Essential	Desirable
▪ Confirmed HIV+ test (2 tests) ▪ If ZDV: hemoglobin ▪ If EFV: pregnancy test	▪ CD4-count ▪ HIV viral load ▪ Total lymphocyte count ▪ Complete blood count ▪ Chest X ray ▪ Sputum smear/culture for TB ▪ Syphilis serology ▪ STI diagnostics ▪ Cryptococcal serology

	▪ Hepatitis serology ▪ Liver function test ▪ Blood chemistry profile ▪ Urine examination

Counseling On Treatment Adherence

Patients starting ART should receive adequate treatment counseling before starting and should be committed to the initiation and continuation of treatment. In particular, the following points should be very well understood:

- ART is not a cure but a lifelong treatment,
- How and when the medications should be taken,
- Potential side effects which are more frequent during the initial first weeks, and what to do in case,
- the potential interactions with other drugs, including traditional medicines, what to stop or substitute when starting ART,
- the need to respect the doses and schedule as prescribed, otherwise the risk of drug resistance will compromise the chances for future treatment,
- Involvement and disclosure to family members about HIV infection status and being on ART

Counseling should assist the patients in identifying methods to support adherence. If possible, a family member should be identified by the patient as a key support person to help remind him/her about the drugs.

Counseling should be flexible and ART may be started at the first visit, if feasible (based on individual readiness and understanding). However, it is strongly recommended to have at least 2 counseling sessions/visits prior to the commencement of ART.

In all cases**, the patient should agree and show a firm commitment for starting ART and for its life long continuation**. ART is seldom an emergency and its use should be initiated only after thoroughly checking patient readiness and clinical indication. Patient readiness refers to the understanding of the information he/she was given by the practitioner/counselor and his/her commitment to adhere to ART

Utilizing an Integrated Medical Approach

ART treatment centers should offer an integrated medical care approach and should not be limited to just provision of ART. Other essential activities to be included are:

- Prophylaxis for opportunistic infections
- Social and psychological support,

- Nutritional support,
- Fostering safe sex practices (behaviour change communication, partner notification and condom promotion)

All adults and adolescents starting ART should be prescribed Trimethoprim-Sulfamethoxazoel for Pneumocystis jirovecii pneumonia and Toxoplasma gondi prophylaxis if symptomatic or if CD4 is less than 200/mm^3

- Trimethoprim/Sulfamethexazole (160mg/800mg)- one tablet daily (preferred) or one tablet three times a week.

Or

- Dapsone 100 mg once daily in case of sulfamethoxazole allergy or contraindication (for PCP)

- Dapsone 200mg + pyrimethamine 75mg + leucovorin 25mg weekly (for Toxoplasma gondi)

Prophylaxis for tuberculosis (TB) is recommended for PPD-positive and HIV-co-infected individuals who do not have active tuberculosis. Prophylaxis for tuberculosis should be prescribed only after excluding active TB (chest X- ray and sputum examination), due to the risk of development of resistance.

- Isoniazid (INH) 5mg/kg or 300 mg once daily plus Pyridoxine 50mg (to prevent neuropathy) for 9 months.
- In cases of suspected multi-drug resistant TB (Isoniazid and Rifampacin resistance) contact or exposure consultation with public health authorities is mandatory. For such cases management by Infectious Disease specialist is recommended.

The use of chemoprophylaxis for major OI (pneumocystis carinii, toxoplasma gondi and TB) should be started as soon as possible if indicated, even before initiating ART.

6. Monitoring Therapy

Follow-up Visits

Once ART is started, an initial schedule for clinical monitoring includes:
- A first follow-up visit at 2 weeks to increase the prescription of Nevirapine to full dose and/or to ensure that there are no treatment related issues.
- Thereafter a visit every three to four months particularly in the first year of treatment.

Monthly visits are strongly encouraged, particularly in the first 3 months of treatment to reinforce adherence, screen for side effects and monitor immune reconstitution syndromes (see below). The visit schedules should be adapted to the patient (for example for those living far from the treatment center).

Follow-up visits should be appointed a week before the ARV drugs are finished.

At each visit, clinical examination should be completed for:
- Assessment for signs and symptoms of potential drug toxicity (table 5),
- Assessment of response to therapy (table 6),
  - Measurement of body weight,
  - Occurrence of symptoms related to OI,
- Assessment and support of adherence (clinically and through CD4 and Viral load testing if available)

For 1st line regimens, the use of any laboratory monitoring test is generally recommended **on a symptom-directed basis**. Routine monitoring of liver functions tests (AST or ALT), Hemoglobin, or pancreatic enzymes (amylase, Lipase) in patients without clinical complaints are not necessary.

Table 4: list of laboratory and other investigations to monitor first line ART

Essential	Desirable
▪ None ▪ Only on a symptom-directed basis	▪ CD4-count (q 3 to 6 months) ▪ HIV viral load (q 3 to 6 months) ▪ HB, Full blood count ▪ Chest X ray (annually) ▪ Liver function tests ▪ Sputum smear for TB (symptoms based) ▪ Syphilis serology (annually) ▪ Hepatitis B & C serology (annually)

Importance of Adherence Counseling at Follow-up Visits

For treatment success, up to 95% of pills should be taken as prescribed with respect to dose and schedule. Poor adherence predisposes the patient to treatment failure, development of resistance and compromises his/her future treatment options. Poor compliance is a public health threat to the emergence and transmission of drug-resistant HIV strains.

Maintaining adherence is a difficult process for the patients everywhere and is influenced by numerous socio-cultural factors. Studies have shown that providers are unable to predict which of their patients are adherent to their medications and which are not. Even in Western countries with surplus availability of resources and support systems patient adherence remains a significant factor in treatment failure and drug resistance. In Pakistan the recent introduction of ART and limited resources pose a challenge to ensuring compliance. Adherence can however be reinforced.

During each follow-up visit specific attention should be paid to reinforcing compliance through adherence counselling. Specific materials have to be developed in local languages and adapted to the local context. Usually adherence counselling lasts up to 30 minutes and is conducted by a nurse, psychologist or counsellor. It is highly recommended that PLWHA be involved as peer counselors.

Adherence counseling should also assist the patient in identifying reasons/barriers to adherence, feasible solutions, and possible support systems (preferably a family member or a community member or another HIV infected person) to provide encouragement and assistance. Adherence implies an engaged and accurate participation of a patient in a plan of care with mutual understanding, consent and partnership. Adherence counseling should be comprehensive, always taking into account that adherence is difficult and that poor adherence can happen to everyone.

Common reasons for poor compliance are:

- **Stock-out of drugs.** This might be related to the disorganized program management which have tremendous consequences on the continuity of the treatment. It leads to unnecessary interruption and change in regimen with rapid emergence of resistance. It might also be related to the patient who was not able to attend the scheduled appointments on time and thus ran out of drugs. For persons living faraway or those who might have transportation problems in attending appointments on time, an extra stock of ARVs might be given for a few days or alternate arrangements explored.
- **Cost for the patient.** The direct and indirect costs for the patient are a major cause of poor adherence. Even if ART is free, the cost of lab monitoring and even the cost of transportation if the patient lives far from the treatment center, might be an obstacle to access follow-up visits for drug renewal.
- **Inadequate understanding of the regimen** (what, when and how to take drugs). For this reason it is highly recommended to simplify the regimen as much as possible. It is also imperative to delay initiation until clear insight has been developed.
- **Misconception about the disease and the treatment.** ART is not a cure and has to be taken lifelong even if the person is healthier.

- **Drug interaction.** ARVs have interaction with other medicines including traditional medicines and the patients should be reminded to take drugs only after consultation with their doctor.
- **Occurrence of side effects.** Simple side effects, like gastro-intestinal symptoms, might lead the patient to stop ART. It is very important when starting the regimen to explain the potential side effects and what to do in case.
- **Depression.** People with depression have more difficulties in taking their medicines. Psychological support to assess and treat depression if needed is necessary.
- **Stigma and secrecy.** People might have difficulties to take their pills during meals because they do not want the others to notice. There are issues of stigmatization and confidentiality within the socio-familial context. Strategies to address these concerns should be discussed in the counseling sessions both with the patient and preferably with close family members.

Assessment of adherence should be done at each visit by:
- Pill count (number of pills remaining since the last visit/ total of pills that should have been taken since the last visit)
- Patient self-report (number of pills actually taken in the last 3-7 days/ number of pills that should have been taken in the last 3-7 days).

Key Points

- To support adherence and maintain confidence in medical services, it is necessary to develop the concept of an integrated medical team (patient, doctor, nurse, counselor, social worker) with respect of confidentiality, where the patient is considered a key player for his/her well-being.
- More frequent visits in the first weeks of treatment and prompt information about the occurrence of specific side effects and their management are highly recommended to improve treatment adherence.
- All drug prescriptions and other related medical information should be given using an adequate language and in a culturally sensitive and empathic manner.
- Use of simplified regimens with low pill burden and with minimal interference in food and social habits, engagement of family members or close friends in the patient's treatment process and use of patient support groups are recommended general strategies to improve ART adherence.
- Psychological and nutritional support has to be integrated during follow-up for patient well being and these factors are critically related to adherence.

Substituting One ARV Drug

Specific drug substitutions should be performed in case of suspected intolerance, toxicity or specific contraindication to one or more components of the 1st line regimen used. In that case only the suspected drug should be changed.

- In case of intolerance, toxicity or contraindication to d4T (Stavudine), it should be replaced by ZDV. The major adverse effects associated with d4T are **neuropathy**

and lipodystrophy (generally after long term use). ZDV can cause GI side effects (self limited) and anemia (sometimes severe).

- In case of intolerance, toxicity or contraindication to NVP, it should be replaced by EFV. The major adverse effect associated with NVP are **hepatitis** and **rash** (sometimes life threatening). EFV can cause CNS effects (generally self limited) and is contraindicated during the 1st trimester of pregnancy because of its teratogenic risk.
- NVP has drug interaction with rifampicin with high risk of hepatitis and should be substituted by EFV during the period with rifampicin containing regimen for TB. If EFV is contraindicated or not available, NVP can be prescribed with rifampicin with close monitoring of clinical hepatitis.
- 3TC in generally is well tolerated and rarely needs to be replaced.

Substituting 1 drug in preferential 1st line regimen

D4T/3TC/Nevirapine

- **D4T - neuropathy or pancreatitis**
  ⇒ D4T for ZDV
- **D4T related lipoatrophy**
  ⇒ D4T for ABC, ZDV or TDF (2nd line drug)
- **NVP related hepatotoxicity**
  ⇒ NVP for EFV
- **NVP severe rash (but not life threatening)**
  ⇒ NVP for EFV
- **NVP related life threatening rash**
  ⇒ NVP for NFV or SQV/r (2nd line drugs)
- **TB ttt with rifampicin**
  ⇒ NVP for EFV

Table 5: Major toxicities and other indications for drug substitution

Regimen	Toxicity or indications	Symptoms directed lab assessment (if available)	Drug substitution
D4T/3TC/NVP (preferential)	▪ D4T related neuropathy or pancreatitis[#]	Amylase, Lipase	▪ Substitute D4T for ZDV
	▪ D4T related lipoatrophy		▪ Substitute D4T for ABC, ZDV or TDF (2nd line drug)*
	▪ NVP related hepatotoxicity	ALT	▪ Substitute NVP for EFV
	▪ NVP severe rash (but not life threatening)		▪ Substitute NVP for EFV
	▪ NVP related life threatening rash		▪ Substitute NVP for NFV or SQV/r (2nd line drugs)
	▪ rifampicin treatment for TB	CXR, sputum	▪ Substitute NVP for EFV**
ZDV/3TC/NVP	▪ ZDV related persistent gastro intestinal intolerance or haematological toxicity	HB, CBC	▪ Substitute ZDV for D4T
	▪ NVP related hepatotoxicity	ALT	▪ Substitute NVP for EFV
	▪ NVP severe rash (but not life threatening)		▪ Substitute NVP for EFV
	▪ NVP related life threatening rash		▪ Substitute NVP for NFV or SQV/r or LPV/r (2nd line drugs)
	▪ rifampicin treatment for TB	CXR, sputum	▪ Substitute NVP for EFV**
D4T/3TC/EFV	▪ D4T related neuropathy or pancreatitis[#]		▪ Substitute D4T for ZDV
	▪ D4T related lipoatrophy		▪ Substitute D4T for ABC, ZDV, DDI or TDF (2nd line drug)*
	▪ EFV related persistent CNS toxicity		▪ Substitute EFV for NVP
	▪ Pregnancy***	Pregnancy test	▪ Substitute EFV for NVP
ZDV/3TC/EFV	▪ ZDV related persistent gastro intestinal intolerance or haematological toxicity	Hb, FBC	▪ Substitute ZDV for D4T
	▪ EFV related persistent CNS toxicity		▪ Substitute EFV for NVP
	▪ Pregnancy***	Pregnancy test	▪ Substitute EFV for NVP

[#] The measurement of blood amylase levels is not useful in many cases. The presumptive diagnosis of pancreatitis should be suspected in front of severe abdominal pain with more than 12 hours of duration without other explained cause and patient should be referred for adequate evaluation.

* if available, D4T can also be substituted for Abacavir, the only ARV drug which have demonstrated partial benefit in lipodystrophy. Substituting D4T will depend on the patient inconvenience. Substituting D4T typically does not reverse lipoatrophy but may slow its progression. Tenofovir (TDF, recommended as 2nd line in Pakistan) can be considered as alternative. In absence, ddI (2nd line regimen in Pakistan) and ZDV are alternatives to consider.

** During TB treatment with rifampicin, nevirapine can be used as an alternative drug, if EFV is contraindicated or not available, but with caution and close clinical monitoring of hepatitis symptoms.

*** Pregnancy should not happen while taking EFV containing regimen. Women should be prescribed reliable contraceptive methods when being started on EFV due to the risk of teratogenicity

Treatment Failure: Switching ART

Treatment failure can be defined clinically by disease progression or immunologically using measurement of CD4 counts and/or virologically by measuring HIV viral load (table 6). Even in resource constrained countries it is cost-effective in the long term to monitor treatment failure through CD4 and viral load assessments instead of clinical disease/symptoms progression.

The criteria for treatment failure suggested to be used currently in Pakistan is clinical. However, tremendous efforts are being made to provide immunological and virological support (i.e CD4 and HIV viral load testing) in ART treatment centers so as to accurately monitor treatment progress and promptly diagnose treatment failures. Adequate adherence to 1st line regimen should be evaluated before switching ART. It must be emphasized that when and where possible treatment failure should be monitored by CD4 and HIV viral load.

Clinical disease should be differentiated from the **immune reconstitution syndrome**, which can be seen early after introduction of ART (generally during the first 3 months and especially in persons with initial CD4 counts <200/mm^3). This syndrome is characterized by the appearance of signs and symptoms of an opportunistic disease after the start of ART in the setting of advanced immunodeficiency, as an inflammatory response to previously undetected subclinical opportunistic infections. It is also possible that this immune reconstitution may lead to the development of atypical presentations of some opportunistic infections. Physicians should not consider immune reconstitution syndrome a clinical progression (worsening) of HIV or as ART failure. OIs should be treated as usual and ART regimen should not change. Caution should be exercised in diagnosing immune reconstitution syndrome in patients who have been on ART > 6 months or more.

In case of treatment failure, all 3 drugs of the initial regimen should be replaced by the 2nd line regimen, after assessment of the level of adherence to the first line regimen. In situations where facilities to perform HIV viral genotype to document type of resistance are available (Reference labs), drug changes should be made according to the resistance pattern in consultation with an Infectious Disease specialist.

Table 6: Clinical and immunological definition of treatment failure in adults and adolescents

Clinical signs of treatment failure (if CD4 not available)	CD4 cell criteria for treatment failure (whenever CD4 monitoring is possible)
▪ Occurrence of new opportunistic infection signifying disease progression, after at least 3 months on treatment. (This must be differentiated form the immune reconstitution syndrome which can occur in the first 3 months of ART) *see text*	▪ Declining CD4 cell numbers to pre-therapy baseline or below without other concomitant infection to explain transient CD4 cell decrease* ▪ > 50% fall from therapy CD4 peak level without other concomitant infection to explain

▪ Recurrence of previous opportunistic infection (except TB since reinfection may occur and clinical evaluation is necessary to define failure in case of TB recurrence) ▪ Onset or recurrence of WHO stage III conditions (including but not restricted to loss of weight, chronic diarrhoea of unknown etiology, prolonged fever of unknown etiology, recurrent invasive bacterial infections or recurrent/persistent mucosal candidiasis)	transient CD4 cell decrease* ▪ If HIV viral load is available, then increasing viral load from an undetectable (<400copies/ul)

* if patient is asymptomatic and treatment failure is being defined by CD4 cell criteria alone, consideration should be given to performing a confirmatory CD4 cell count if resources permit.

When and If Stopping ART

ARV treatment should be stopped only for a limited number of reasons:

- If adequate treatment adherence cannot be achieved despite all efforts
- Temporary suspension in situations of life threatening ART related adverse effects or when the exact causative drug cannot be easily identified.
- Patient wants to discontinue ART

The occurrence of opportunistic infections is not an indication to interrupt treatment, but if necessary to stop, ART should be reintroduced only after clinical stabilization of the patient.

If definitive or temporarily interruption of ART is indicated, all three drugs must be stopped simultaneously.

7. Second Line ART Regimens For Treatment Failure

In case of treatment failure, 2 or more drugs of the initial regimen should be replaced by the 2nd line regimen, after thorough assessment of patient adherence to the 1st line regimen. Switching ART for failure and starting a 2nd line regimen generally requires referral and/or involvement of an infectious disease specialist in patient care management.

The suggested preferential 2nd line regimen in Pakistan is Tenofovir (TDF) + ddI (in enteric coated formulation) + Nelfinavir (NFV). Saquinavir boosted ritonavir (SQV/r) or Lopinavir/ritonavir (LPV/r) are suggested as suitable alternative PI drug in case of NFV intolerance or if reliable cold chain facilities are available. Indinavir (without rotonavir boosting) is another less preferred option in settings without safe cold chain storage facilities. However, the food restriction and development of renal stones limits the utility of IDV except in situations where other options cannot be tolerated. The available 2nd line regimens are:

- **TDF or ABC +ddI+ NFV (preferential)**
- TDF or ABC +ddI+SQV/r or LPV/r
- TDF or ABC + ddI+ IDV

2nd line regimens have a high pill burden and increased costs.

The conventional ddI dose should be reduced to 250 mg (> 60 kg) or 125 mg (< 60 mg) because drug interaction with TDF.

TDF can cause renal toxicity and ddI can be associated with neuropathy, diarrhea and pancreatitis. SQV/r can promote GI intolerance and dyslipidemia. NFV can cause diarrhoea. Both PI options currently present high pill burden.

During 2nd line treatment, fasting glucose and lipids levels should be evaluated at baseline and periodically thereafter (1-2 times/year) because PI use is associated with development of hyperglycemia (diabetes) and increased lipids. . Baseline and periodic BUN (blood urea nitrogen) and creatinine measurement is also recommended if TDF is used. Other lab tests for toxicity monitoring are mandatory only if specific related symptoms are present.

In 2nd line regimens, the drugs should preferentially be taken with food, with exception of ddI that should be ingested on an empty stomach (1/2 hour before or 2 hours after food).

Table 7: Description of ARV second line drugs

Drugs	dose	Special consideration	use in pregnant women	use with TB ttt	Adverse effects	Essential lab monitoring (otherwise symptoms directed)
Tenofovir (TDF)	300 mg od	With food (fat meal)	Use with caution***	Yes	Gastrointestinal intolerance Renal toxicity	BUN (blood urea nitrogen) or Creatinine
ddI (enteric coated EC formulation)	< 60kg: 125mg od* > 60 kg: 250mg od*	Empty stomach (1/2 h before or 2 h after meals)	Yes	Yes	Pancreatitis Peripheral neuropathy Nausea, diarrhea Lactic acidosis with hepatic steatosis (rare)	
Nelfinavir (NFV)	1250 mg bd	With food	Yes	Yes	Diarrhea, hyperglycaemia, fat redistribution and lipid abnormalities	Fasting glycemia and lipids
Saquinavir boosted by ritonavir SQR/r**	1000mg/100mg bd or 1600mg/200mg od	**Cold chain#** With food	Yes	yes	Gastrointestinal intolerance, nausea, vomiting, headache, elevated transaminases enzymes, hyperglycaemia, fat redistribution and lipid abnormalities	Fasting glycemia and lipids
Lopinavir/ritonavir (LPV/r)	LPV 400mg/100 mg ritonavir bid	**Cold chain#** With food	Use with caution***	Yes	Gastrointestinal intolerance, nausea, vomiting, headache, elevated transaminases enzymes, hyperglycaemia, fat redistribution and lipid abnormalities (increased Triglycerides)	Fasting glycemia and lipids

Indinavir (IDV)	800mg three times/day (every 8 hours)	Empty stomach (1/2 h before or 2 h after meals	Use with caution***	Yes	Renal stones, Gastrointestinal intolerance, nausea, indirect hyperbilirubinemia, hyperglycaemia, fat redistribution and lipid abnormalities	Fasting glycemia and lipids

* Conventional ddI doses reduced by half because of drug interaction with TDF
** Both hard gel and soft gel capsule formulations can be used when SQV is combined with RTV
*** TDF, LPV/r, IDV not fully evaluated during pregnancy
# The cold chain specificities for storage in pharmacies is between 2 to 8 °C. For patient use or in situations where the refrigeration is not possible, the temperature should be maintained below 25 °C and it is safe for until 3 months. In temperatures > 25 C the shelf life is < 30 days. SQ

8. Considerations for ART Use in Special Patient Populations.

Women of Reproductive Age and Pregnant Women

When initiating ART for women of reproductive age, the indications for starting therapy are the same as for other adults. However, the ARV regimen selection should account for the possibility of planned or unplanned pregnancy. EFV should be avoided for the woman who wishes to become pregnant or who does not use effective and consistent contraception.

In pregnant women, d4T/3TC/NVP is the preferential 1st line ART regimen. Symptomatic NVP-associated hepatic toxicity or serious rash, although uncommon, is more frequent in women than in men and is more likely to be seen in women with comparatively elevated CD4 cell counts (> 250/mm^3). It is not known if pregnancy further predisposes women to such toxicities but cases have been reported in pregnant women. EFV is strongly contraindicated during the 1st trimester but can be used after the second trimester if other alternatives are not feasible or available.

For 2nd line regimen, NFV, LPV/r, IDV or SQV/r and ddI can be used during pregnancy with close monitoring for toxicities and treatment response. TDF has not fully been evaluated in pregnant women and should only be used with caution.

PMTCT (Prevention of mother-to-child transmission), ART is recommended in all pregnant women, regardless of clinical, virological or immunological parameters, for the purpose of PMTCT. Anti-retroviral drugs should be used within a framework of prevention, treatment and care both to prevent transmission to the child and to maintain the health of the mother. Some recommended regimens are:

Clinical Situation	Recommendation
HIV infected pregnant women with indications for initiating ART	**Women** 1st line: ZDV+3TC+NVP or d4T+3TC+NVP Alternative: ZDV+3TC+NFV or ZDV +3TC+SQV/r **Infants:** ZDV for one week or single dose NVP or single dose NVP+ZDV for one week.
HIV infected pregnant women without indications for ART	**Women** If ART is available the strongly recommended regimen even in such a clinical situation is: 1st line: ZDV+3TC+NVP or d4T+3TC+NVP 2nd line: ZDV+3TC+NFV or ZDV +3TC+SQV/r

	In situations where ART is not available or feasible, alternative regimens are (these single or 2 drug regimens are associated with increased risk of resistance) • ZDV starting at 28 weeks or as soon as feasible thereafter; continue ZDV during labor, plus single dose NVP at the onset of labor. or • ZDV starting at 28 weeks or as soon as feasible thereafter; continue in labor or • ZDV+ 3TC starting at 36 weeks or as soon as feasible thereafter; continue in labor and for one week post partum or • Single dose NVP **Infants:** • ZDV for one week or single dose NVP or • single dose NVP+ZDV for one week.
Women in labor known to be HIV infected who have not received ART	**Women** • single dose NVP or • ZDV+ 3TC in labor; and for one week postpartum **Infants** • Single dose NVP or ZDV+3TC for one week
Infants born to HIv infected women who have not received any ART	**Infants** • Single dose NVP as soon as possible after birth +ZDV for one week If the regimen is started more than 2 days after birth, it is unlikely to be effective.

Pregnant women who are started on ART for the sole indication of PMTCT may choose to stop ART after delivery. However, if ART includes NVP, then consultation with an Infectious Disease specialist is recommended when stopping therapy to avoid development of resistance due to the long half-life of NVP.

Tuberculosis (TB/HIV Co-infection)

Due to the frequency of HIV/TB co-infection, many patients who are candidates for ART will have active TB. In addition, patients already receiving ART may develop clinical TB. Effective treatment and control of TB is a central priority when developing treatment strategies for co-infected patients.
The management of HIV and TB co-infection is complicated because of the high pill burden and adherence, rifampicin interaction with NVP and PI, and drug toxicity.

In all diagnosed TB cases, TB treatment following the DOTS strategy should be initiated promptly. . The two major issues in the clinical management of patients with HIV and TB are **when to start ART** and **which regimen to use**.

The optimal time in patients with TB is not known.

- ART is recommended for all patients with TB at high risk of HIV disease progression and mortality (CD4 count <200 cells/mm^3) and should be considered even in patients with CD4 < 350 cells/mm^3.
- In the absence of CD4 cell-count, ART is recommended for all patients with TB.
- ART should be started as soon as the TB treatment is tolerated (i.e within 2 weeks - 2 months of beginning TB treatment).

In TB/HIV co-infection, the preferential 1st line regimen is d4T/3TC/EFV. EFV should be used in its regular dose. NVP can be used as an alternative drug if EFV is not available or contra-indicated, but with caution and with a close clinical monitoring of hepatitis symptoms. After completing rifampicin based TB treatment, NVP can replace EFV using full dose without any need of dose escalation schedule.

In 2nd line regimens NFV should not be used with Rifampacin containing TB regimens. LPV/r (higher doses needed, must consult an Infectious Disease specialist) or SQV/r can be used with TB regimens containing rifampicin but require close monitoring.

Hepatitis B (HBV)/Hepatitis C (HCV) Co-infections

In HIV-Hepatitis B or Hepatitis C co-infected patients, the decision about NNRTI use in the 1st line regimen should be done taking in consideration the patient clinical status and the presence of clinical or laboratory evidence of active liver disease. The presence of HBV or HCV seropositivity is not a contraindication to NVP, but a close clinical monitoring is generally recommended.

All ARVs should be used with caution in patients with evidence of hepatic dysfunction (elevated AST, ALT or cirrhosis) and ARVs with major hepatotoxic risk (NVP in the first 6-8 weeks of treatment and RTV in full dose) should be avoided.

As 3TC and TDF have anti-HBV activity, 1st line regimen must include 3TC, and 2nd line regimen should preferably include TDF, for patients with hepatitis B infection to avoid flares.

All patients with HBV or HCV should be evaluated for treatment of their hepatitis infections as well.

Injecting Drug Users (IDUs)

Although treatment of HIV disease in this population can be successful, IDUs with HIV disease present special treatment challenges. These include complicating co-morbid conditions, limited access to HIV care, inadequate adherence to therapy, medication side effects and toxicities, and the need for substance abuse treatment. While some drug users can control their drug use sufficiently to engage in care successfully, treatment of substance abuse is a prerequisite for successful ART. Enrolment in and successful completion of drug rehabilitation programs is mandated prior to initiation of ART in drug users.

In IDUs on Methadone substitution treatment programs, the preferential 1st line and 2nd line PI based regimens are clinically problematic (i.e NVP, EFV, LPV/r, and NFV all reduce methadone levels leading to opiate withdrawal). Buprenorphine, a partial opiate agonist, is increasingly being used for opiate abuse. However, there is only limited information showing no adverse interaction between Buprenorphine and ARV.

Children

These guidelines mainly focus on ART treatment in adolescents and adults. Readers are recommended to refer to specific pediatric guidelines for more information on ART for children (available at WHO website: www.who.org; Pediatric Guidelines)

The laboratory diagnosis of HIV infection in infants aged less than 18 months is difficult because of the persistence of maternal antibodies. It requires an HIV viral load to confirm the infection. Therefore the recommendations to initiate ART in children are dependent on the age and on the availability of virological tests (table 9).

Formulations for children are not available for all drugs. Solid formulation presents problems with swallowing in young children. Dosing must be adjusted as child grows. Splitting of adult dose tab/caps might be the only way to provide therapy to children with the risk of under or overdosing.

- In HIV+ children, the preferential 1st line regimen is the same as in adults (d4T/3TC/NVP).

ZDV can be used safely in children. EFV is approved for use in children older than 3 years old.

For 2nd line regimen, SQV/r should be used only in children with body weight greater than 25 kg. NFV, LPV/r and IDV can be used in children. TDF is not approved for pediatric use and should be substituted by Abacavir.

ART regimen for children

First line regimen
- D4T+3TC+NVP in fixed drug combination (preferential)
- ZDV+3TC+NVP
- D4T+3TC+EFV (if > 3 years old)
- ZDV+3TC+EFV (if > 3 years old)

Second line regimen
- ZDV+ 3TC + NFV or LPV/r
- ZDV+ddI + NFV
- ABC+ddI+SQV/r (if weight ≥ 25 kg)

Laboratory assessments for children on ART are the same as those recommended for adults. In addition to the clinical assessments recommended for adults, the clinical monitoring of ART in children should include:
- Nutrition and nutritional status,
- Weight and height growth,
- Developmental milestones,
- Neurological symptoms.

Table 8: Pediatric drug doses

Drug	Dose
D4T	▪ <30 kg: 1mg/kg bd ▪ 30-60 kg: 30 mg bd
3TC	▪ <30 days: 2 mg/kg bd ▪ ≥30 days and <60 kg: 4mg/kg bd
ZDV	▪ <4 weeks: 4mg/kg bd ▪ 4 weeks to 13 years: 180 mg/ m^2 bd
ddI	▪ <3 months: 50 mg/ m^2 bd ▪ 3 months to 13 years: 90-120 mg/ m^2 bd or 240 mg/ m^2 od
Abacavir	▪ <16 years or <37.5 kg: 8 mg/kg bd
Nevirapine	▪ 15-30 days: o 5 mg/kg od for 2 weeks o then 120 mg/ m^2 bd for 2 weeks o then 200 mg/ m^2 bd ▪ >30 days to 13 years o 120 mg/ m^2 od for 2 weeks o then 120-200 mg/ m^2 bd
Efavirenz (if > 3 years old)	▪ 10-<15 kg: 200mg od ▪ 15-<20 kg: 250 mg od ▪ 20-<25 kg: 300 mg od ▪ 25-<33 kg: 350 mg od ▪ 33-<40 kg: 400 mg od
Nelfinavir LPV/r IDV	▪ <1 year: 50 mg/kg td or 75 mg/kg bd ▪ 1 to <3 year: 55-65 mg/kg bd ▪ 7-<15kg : 13mg/3.25mg per kg twice daily with food ▪ 15-<50kg: 11mg/2.75 mg per kg twice daily with food ▪ >50 kg: 533mg/133mg per kg twice daily with food

Table 9: WHO recommendations for initiating ART in infants and children

CD4 testing	Age	HIV diagnostic testing	Treatment recommendation
If CD4 testing is available	< 18 months	HIV virological testing not available	WHO Paediatric Stages II and III disease with CD4 <20%
		Positive HIV virological test	WHO Paediatric Stage III irrespective of CD4 % WHO Paediatric Stage II disease with consideration of using CD4 <20% to assist in decision-making WHO Paediatric Stage I with CD4 <20%
	≥18 months	HIV antibody seropositive	WHO Paediatric Stage III disease, irrespective of CD4 % WHO Paediatric Stage II disease, with consideration of using CD4 <15% to assist in decision-making WHO Paediatric Stage I disease with CD4 <15%
If CD4 testing is not available	<18 months	HIV virological testing not available	Treatment not recommended
		Positive HIV virological test	WHO Paediatric Stage III, irrespective of total lymphocyte count WHO Paediatric Stage II disease, with consideration of using total lymphocyte count <2500/mm^3 to assist in decision-making
	≥ 18 months	HIV antibody seropositive	WHO Paediatric Stage III irrespective of total lymphocyte count WHO Paediatric Stage II disease, with consideration of using total lymphocyte count <1500/mm^3 to assist in decision-making

9. Post Exposure Prophylaxis (PEP) After Exposure to HIV

What is PEP?

Prophylaxis means disease prevention. PEP means taking ARV as soon as possible after exposure to HIV, so that the exposure will not result in HIV infection. PEP should begin within 24-36 hours and should continue for 4 weeks.

Who Should Use PEP?

Occupational Exposure:
An workplace exposure is defined as one that may place a worker at risk of HIV infection through percutaneous injury, contact of mucous membrane or skin (chapped or abraded) with blood, tissue or other body fluids to which universal precautions apply from a person known or suspected to be HIV positive.

Most exposures do not result in infection. Average risk of HIV infection after an occupational exposure is generally low:

Clinical Situation	**Risk**
Risk with Small amount of blood on intact skin	no risk
Risk with needle stick injury	1 in 300 (0.003%, dependent on type of needle i.e solid versus hollow bore, percutaneous)
Exposure of mucous membrane	1 in 1000 (0.001%)
Risk with broken skin	1 in 1000 (0.001%)

Other Non- Occupational Exposure:
Are generally considered to be the following:

- Sexual assault or rape
- Infants exposed to breast milk from HIV infected mothers

, Factors Affecting Transmission:

- Amount of blood in the exposure
- Higher viral load >100,000 (greater risk)
- Advanced AIDS in source patient

What Actions to Undertake Upon Exposure?

- Do not panic
- Do not put the cut/pricked finger into your mouth.
- Immediately wash the exposed area thoroughly with soap and water. No added benefit in using bleach or anti-septic.
- Promptly report exposure to relevant authorities or (NACP) 051-9255096
- Determine the HIV status of the exposure source person (i.e HIV viral load, CD4, HIV +, HBV and HCV)
- Decision to initiate PEP.

- If yes to initiating PEP then recommend starting Post exposure prophylaxis as soon as possible within 72 hours (<3 days)

Regimens for PEP:

For low risk exposures :

2 drug regimen :
- ZDV+3TC

For high risk exposures :

Expanded 3 drug regimen :
- ZDV + 3TC + EFV or LPV/r

Decisions to initiate PEP should be made after carefully evaluating the exposure and prefereably in consultation with an Infectious Disease specialist. Particularly in rape cases the use of EFV is contraindicated and an Infectious diseases specialist must be copnsulted. The following table 4 and 5 will assist in categorizing the type of exposure and the need for PEP :

TABLE 4. Recommended HIV postexposure prophylaxis for percutaneous injuries

	Infection status of source				
Exposure type	HIV-Positive Class 1*	HIV-Positive Class 2*	Source of unknown HIV status†	Unknown source§	HIV-Negative
Less severe¶	Recommend basic 2-drug PEP	Recommend expanded 3-drug PEP	Generally, no PEP warranted; however, consider basic 2-drug PEP** for source with HIV risk factors††	Generally, no PEP warranted; however, consider basic 2-drug PEP** in settings where exposure to HIV-infected persons is likely	No PEP warranted
More severe§§	Recommend expanded 3-drug PEP	Recommend expanded 3-drug PEP	Generally, no PEP warranted; however, consider basic 2-drug PEP** for source with HIV risk factors††	Generally, no PEP warranted; however, consider basic 2-drug PEP** in settings where exposure to HIV-infected persons is likely	No PEP warranted

* HIV-Positive, Class 1 — asymptomatic HIV infection or known low viral load (e.g., <1,500 RNA copies/mL). HIV-Positive, Class 2 — symptomatic HIV infection, AIDS, acute seroconversion, or known high viral load. If drug resistance is a concern, obtain expert consultation. Initiation of postexposure prophylaxis (PEP) should not be delayed pending expert consultation, and, because expert consultation alone cannot substitute for face-to-face counseling, resources should be available to provide immediate evaluation and follow-up care for all exposures.

† Source of unknown HIV status (e.g., deceased source person with no samples available for HIV testing).

§ Unknown source (e.g., a needle from a sharps disposal container).

¶ Less severe (e.g., solid needle and superficial injury).

** The designation "consider PEP" indicates that PEP is optional and should be based on an individualized decision between the exposed person and the treating clinician.

†† If PEP is offered and taken and the source is later determined to be HIV-negative, PEP should be discontinued.

§§ More severe (e.g., large-bore hollow needle, deep puncture, visible blood on device, or needle used in patient's artery or vein).

TABLE 5. Recommended HIV postexposure prophylaxis for mucous membrane exposures and nonintact skin* exposures

	Infection status of source				
Exposure type	HIV-Positive Class 1†	HIV-Positive Class 2†	Source of unknown HIV status§	Unknown source¶	HIV-Negative
Small volume**	Consider basic 2-drug PEP††	Recommend basic 2-drug PEP	Generally, no PEP warranted; however, consider basic 2-drug PEP†† for source with HIV risk factors§§	Generally, no PEP warranted; however, consider basic 2-drug PEP†† in settings where exposure to HIV-infected persons is likely	No PEP warranted
Large volume¶¶	Recommend basic 2-drug PEP	Recommend expanded 3-drug PEP	Generally, no PEP warranted; however, consider basic 2-drug PEP†† for source with HIV risk factors§§	Generally, no PEP warranted; however, consider basic 2-drug PEP†† in settings where exposure to HIV-infected persons is likely	No PEP warranted

* For skin exposures, follow-up is indicated only if there is evidence of compromised skin integrity (e.g., dermatitis, abrasion, or open wound).

† HIV-Positive, Class 1 — asymptomatic HIV infection or known low viral load (e.g., <1,500 RNA copies/mL). HIV-Positive, Class 2 — symptomatic HIV infection, AIDS, acute seroconversion, or known high viral load. If drug resistance is a concern, obtain expert consultation. Initiation of postexposure prophylaxis (PEP) should not be delayed pending expert consultation, and, because expert consultation alone cannot substitute for face-to-face counseling, resources should be available to provide immediate evaluation and follow-up care for all exposures.

§ Source of unknown HIV status (e.g., deceased source person with no samples available for HIV testing).

¶ Unknown source (e.g., splash from inappropriately disposed blood).

** Small volume (i.e., a few drops).

†† The designation, "consider PEP," indicates that PEP is optional and should be based on an individualized decision between the exposed person and the treating clinician.

§§ If PEP is offered and taken and the source is later determined to be HIV-negative, PEP should be discontinued.

¶¶ Large volume (i.e., major blood splash).

Ethical Considerations: Equity, Stigma and Gender Issues

Stigma and discrimination toward PLWHA and high risk population remain very high among health staff in the public and private sector. Stigma and discrimination might represent an obstacle in accessing VCT and care. Codes of conduct and medical responsibility need to be enforced among health staff. ART treatment centers should advocate for solidarity, tolerance, compassion and equity in access to care.

A shared confidentiality needs to be respected among the medical team, including lab technicians. Security measures should be ensured for medical files with restricted access and secure storage. In case, computerisation of individual data should use an identification number and the names of the patients should not be entered.

The consultation workshop stressed the high vulnerability of women and children in the dominated patriarchal society. In the socio-cultural context of Pakistan, medical care of women and children is dependent on decisions made by male members of the family (husband, father, brother). An integrated family approach needs to be promoted in accessing VCT and care services. During VCT or HIV related care for men, it is part of the medical responsibility to repeatedly request the participation of the wife and children and to promote VCT and HIV care for the full nuclear family.

It is necessary to emphasize the importance of preventive education during medical care. Behavior change communication and condom promotion have to be integrated in ART services.

10. Annexes

References

- Scaling up antiretroviral therapy in resource-limited settings: Treatment guidelines for a public health approach. WHO 2003 revision.

  - WHO Consultation on Technical and Operational Recommendations in Scale up of Laboratory Services and Monitoring HIV therapy in resource poor settings (Geneva 13-15 December 2004)

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- Chronic HIV care with ARV therapy. Interim guidelines for 1st level facility health workers. WHO 2004.

- Access to HIV/AIDS drugs and diagnostics of acceptable quality. List of prequalified products (WHO 8/2004). http://mednet3.who.int/prequal/hiv/hivdefault.htm

- A public health approach for scaling-up ARV treatment. A toolkit for programme managers. WHO 2004.

- Treating 3 million by 2005. Making it happen. WHO 2004.

- Technical and Operational Recommendations to achieve 3by5. WHO 2004.

- Working document on monitoring and evaluating of national ART programmes in the rapid scale-up to 3 by 5. (WHO 2004)

- CDC Guidelines on Antiretroviral use in Adults and Adolescents (2005)

Appendix 2: List of Antiretroviral Drugs

Drug	Formulation (mg) adolescents and adults	Dose adolescents and adults	Special Considerations	Adverse effects
Nucleoside Reverse transcriptase inhibitors				
Zidovudine(ZDV)	Tablet : 100,250, 300* Oral Solution: 50mg/5ml	300 mg bid	With or without food	Anaemia, neutropenia, Gastrointestinal intolerance, Headache, insomnia, myopathy Lactic acidosis with hepatic steatosis (rare)
Lamivudine (3TC)	Tablet : 150 Oral Solution: 50mg/5 ml	150 mg bid	With or without food	Minimal toxicity Lactic acidosis with hepatic steatosis (rare)
Didanosine (ddI)	Tablet: 250, 400	<60 kg:125 mg bd or 250 mg od >60 kg: 200 mg bd or 400 mg od	empty stomach (1/2h prior or 2 h after meals) doses reduced by half with TDF	Pancreatitis Peripheral neuropathy Nausea, diarrhea Lactic acidosis with hepatic steatosis (rare)
Stavudine (d4T)	Capsule: 30,40 Oral solution: 5mg/ml	<60kg:30 mg bd >60 kg:40 mg bd	With or without food	Pancreatitis Peripheral neuropathy Lactic acidosis with hepatic steatosis(rare) Lipoatrophy
Abacavir (ABC)	Tablet: 300	300 mg bd	With or without food	Hypersensitivity reaction(can be fatal) Fever, rash, fatigue Nausea, vomiting, anorexia Respiratory symptoms(sore throat, cough) Latic acidosis with hepatic steatosis (rare)
Emtricitabine (FTC)	200	200 mg od	With or without food	Headache, nausea, skin rash and discoloration Lactic acidosis with hepatic steatosis(rare)
Non nucleoside reverse transcriptase inhibitors				
Efavirenz (EFV)	Capsule 50 mg, 100 mg, 200 mg	600 mg od	With or without food Bed time administration to avoid CNS symptoms	CNS Symptoms: dizziness, somnolence, insomnia, confusion, hallucinations, agitation Elevated transaminase levels Skin rash
Nevirapine (NVP)	Tablet 200 mg, oral suspension 50mg/ 5ml	200 mg od x 14 days then 200 mg bd	With or without food	Skin rash, Stevens-Johnson Syndrome Elevated serum aminotransferase levels Hepatitis, life-threatening Hepatic toxicity

Protease inhibitors				
Indinavir (IND)	Capsule: 100, 200, 333, 400 mg	400 mg q8h	Empty stomach Lot of fluid intake (2 liters per day)	Nephrolithiasis, gastrointestinal intolerance, hyperglycaemia, fat redistribution and lipid abnormalities, headache, dizziness, rash, thrombocytopenia, alopecia, bleeding in haemophilia patients
Nelfinavir (NFV)	Tablet: 250 mg	750 mg tds 1250 mg bd	With food	Diarrhoea, hyperglycaemia, fat redistribution and lipid abnormalities
Saquinavir SGF (SQV)	Capsule gel: 200 mg	1200 mg tds	With food	Gastrointestinal intolerance, nausea, vomiting, headache, elevated transaminase enzymes, hyperglycaemia, fat redistribution and lipid abnormalities
Ritonavir	Capsule: 100 mg Oral Solution: 400 mg/ 5 ml	600 mg bd	Use only as booster PI	Gastrointestinal intolerance, nausea, vomiting, paresthesia, hepatitis and pancreatitis, hyperglycaemia, fat redistribution and lipid abnormalities
Lopinavir + ritonavir (LPV/r)	Capsule: 133.3 + 33 mg 400 mg/100 mg bd Syrup: 400 mg. 5 ml + 600 mg/5 ml	533 mg/133 mg bd when combined with EFV/NVP	With food	GI intolerance, nausea, vomiting, elevated transaminase enzymes, hyperglycaemia, fat redistribution and lipid abnormalities
Atazanavir	200mg	400mg od	With food	Insufficient data Allergy, hyperglycemia, jaundice, GI intolerance, pain, cough, depression, lipodystrophy
Amprenavir	150 mg	1200 mg bd	With or without food	Well tolerated abdominal pain, diarrhea, hyperglycemia, nausea, oral paresthesia, skin rash, and vomiting skin rash hyperglycemia, lipodystrophy
Nucleotide reverse transcriptase inhibitor				
Tenofovir(TDF)	300 mg	300 mg od	With food	abdominal pain, anorexia, asthenia, diarrhea, dizziness, dyspnea, flatulence, headache, hypophosphatemia, lactic acidosis, nausea, pancreatitis, renal impairment, rash, vomiting Lactic acidosis with hepatic steatosis (rare)

* ZDV available at this dosage as a coformulation with 3TC

Appendix 3: WHO Revised Clinical Staging in Adults and Adolescents

(For use in those 15 years of age or more with positive HIV antibody test or other laboratory evidence of HIV infection)

PRIMARY HIV INFECTION
Unrecognized Acute retroviral syndrome[i]
CLINICAL STAGE 1
Asymptomatic Persistent generalized lymphadenopathy (PGL)
CLINICAL STAGE 2
Moderate unexplained weight loss (<10% of presumed or measured body weight) Recurrent upper respiratory tract infections (sinusitis, bronchitis, otitis media, pharyngitis) Herpes zoster Angular cheilitis Recurrent oral ulcerations Papular pruritic eruptions Seborrhoeic dermatitis Fungal nail infections of fingers
CLINICAL STAGE 3
Conditions where a presumptive diagnosis can be made using clinical signs or simple investigations Severe weight loss (>10%presumed or measured body weight) Unexplained chronic diarrhoea for longer than one month Unexplained persistent fever (intermittent or constant for longer than 1month) Oral candidiasis Oral hairy leukoplakia Pulmonary tuberculosis[2] (diagnosed in last two years) Severe presumed bacterial infections (e.g. pneumonia, empyema, pyomyositis, bone or joint infection, meningitis, bacteremia) Acute necrotizing ulcerative stomatitis, gingivitis or periodontitis
Conditions where confirmatory diagnostic testing is necessary
Unexplained Anaemia (<8gm/dl), neutropenia (<1,000/$mm^{3)}$ or thrombocytopenia (<50,000/ $mm^{3)}$ for more than 1 month
CLINICAL STAGE 4
Conditions where a presumptive diagnosis can be made using clinical signs or simple investigations: HIV wasting syndrome Pneumocystis pneumonia Recurrent severe or radiological bacterial pneumonia Chronic Herpes simplex infection; (orolabial, genital, or anorectal of more than 1 month duration, or visceral of any duration) Oesophageal Candidiasis Extrapulmonary tuberculosis Kaposi's sarcoma CNS toxoplasmosis HIV encephalopathy ***Conditions where confirmatory diagnostic testing is necessary:*** Extrapulmonary Cryptococcsis including meningitis Disseminated non-tuberculous mycobacteria infection Progressive multifocal leukoencephalopathy (PML) Candida of trachea, bronchi, or lungs Cryptosporidiosis Isosporiasis Cytomegalovirus infection (retinitis or of an organ other than liver, spleen, or lymph nodes) Any disseminated mycosis (e.g. Histoplasmosis, Coccidiomycosis, Penicilliosis) Recurrent non-typhoidal salmonella septicaemia Lymphoma (Cerebral or B cell non-Hodgkin's) Invasive cervical carcinoma Visceral Leishmaniasis,

Explanatory Notes

The clinical staging system for adults and adolescents is designed to:

1. Be used where HIV infection is confirmed by HIV antibody or virological testing

2. Harmonize with immunological and HIV/AIDS surveillance definitions to enable monitoring of trends in the magnitude and severity of HIV/AIDS related disease.

3. Classify disease in a progressive sequence from least to most severe, with each higher clinical stage having a poorer prognosis. Once a stage 3 clinical event has occurred, the prognosis remains that of stage 3 and does not change, even with resolution of the original condition.

4. Provide simple guidance to assist clinical care providers on when to start, substitute, switch or stop ARV therapy in HIV infected adults and adolescents, or trigger referral as outlined in WHO ART guidelines for a public health approach.

5. Be largely used with reference to CURRENT clinical events, meaning clinical events that have been diagnosed or are being managed at this episode.

6. Be considered in relation to previous clinical events, such as reported TB, severe pneumonia, PCP or other conditions. This is RETROSPECTIVE clinical staging and requires caution. **Note:** Reported history of a stage 3 or stage 4 clinical event should have immediate assessment by, or referral to, HIV care providers able to initiate ARV treatment.

7. Be used once a patient is started on ART. ART improves the prognosis regardless of initial clinical stage.
8.
9. Be used to guide clinicians in assessing the response to ARV treatment, particularly where viral load and or CD4 counts/or percent are not widely or easily available.
   - New or recurrent stage 4 events may suggest failure of response to treatment,
   - New or recurrent stage 2 or 3 events may suggest inadequate response to treatment, potentially due to poor adherence.

   However further evidence is required to determine the significance of staging events once on ART

   Note: Clinical events in the first 3 months of starting ART may be due to immune restoration disease (IRD) not a poor response to ART.

   Note: Total lymphocyte count (TLC) is not currently recommended for monitoring therapy.

   Note: Encourage clinical care providers to consider diagnostic testing for HIV for patients with the clinical events suggestive of HIV disease. Stage 3 or 4 events should prompt the offer of HIV diagnostic testing.

Appendix 4: WHO Classification in Children < 13 years old

(For use in those under 15 years with confirmed laboratory evidence of HIV infection; HIV Antibody where age >18 months, virological or P24 Ag testing for those age <18 months)

STAGE 1

- Asymptomatic
- Persistent generalized lymphadenopathy (PGL)
- Hepatosplenomegaly

STAGE 2

- Papular pruritic eruptions
- Seborrhoeic dermatitis
- Extensive Human papilloma virus infection
- Extensive Molluscum infection
- Fungal nail infections
- Recurrent oral ulcerations
- Lineal Gingival Erythema (LGE)
- Angular chelitis
- Parotid enlargement
- Herpes zoster
- Recurrent or chronic upper respiratory tract infections (otitis media, otorrhoea, sinusitis,)

STAGE 3

Conditions where a presumptive diagnosis can be made using clinical signs or simple investigations

- Moderate unexplained malnutrition[ii] not adequately responding to standard therapy
- Unexplained persistent diarrhoea (14 days or more)
- Unexplained persistent fever (intermittent or constant, for longer than 1month)
- Oral candidiasis (outside neonatal period)
- Oral hairy leukoplakia
- Acute necrotizing ulcerative gingivitis/periodontitis
- Pulmonary tuberculosis[iii]
- Severe recurrent presumed bacterial pneumonia

Conditions where confirmatory diagnostic testing is necessary

- Lymphoid interstitial pneumonitis (LIP)
- Unexplained Anaemia (<8gm/dl), neutropenia (<1,000/$mm^{3)}$ or thrombocytopenia (<50,000/ $mm^{3)}$ for more than 1 month
- Chronic HIV associated lung disease including brochiectasis

STAGE 4

Conditions where a presumptive diagnosis can be made using clinical signs or simple investigations:

- Unexplained severe wasting or severe malnutrition[iv] not adequately responding to standard therapy
- Pneumocystis pneumonia
- Recurrent severe presumed bacterial infections (e.g. empyema, pyomyositis, bone or joint infection, meningitis, but excluding pneumonia)
- Chronic Herpes simplex infection; (orolabial or cutaneous of more 1 month duration, visceral of any duration)
- Extrapulmonary tuberculosis
- Kaposi's sarcoma
- Oesophageal Candidias
- CNS Toxoplasmosis (outside the neonatal period)
- HIV encephalopathy

Conditions where confirmatory diagnostic testing is necessary:

- CMV infection (CMV retinitis or infection of organ other than liver, spleen, or lymph nodes onset at age 1 month or more)
- Cryptococcal meningitis (or other extrapulmonary disease)
- Any disseminated endemic mycosis(e.g. extra-pulmonary Histoplasmosis, Coccidiomycosis, Penicilliosis)
- Cryptosporidiosis
- Isosporiasis
- Disseminated non-tuberculous mycobacteria infection
- Candida of trachea, bronchi or lungs
- Acquired HIV related rectal fistula
- Cerebral or B cell non-Hodgkin's Lymphoma
- Progressive multifocal leukoencephalopathy (PML)
- HIV related cardiomyopathy or HIV related nephropathy

Presumptive Stage 4 diagnosis in children less than 18 months

The presumptive diagnosis is designed for use where access to confirmatory diagnostic testing for HIV infection using virological or P24 Antigen for infants and children less than 18 months is not readily available. It is not recommended for use by clinical care providers who are not trained on ART , accredited or certified and experienced in HIV care, and must be accompanied by immediate efforts to confirm the HIV diagnosis with the best nationally or locally available test.

Presumptive Stage 4 diagnosis in children less than 18 months old where virological confirmation of infection is not available

HIV seropositive infant less than 18 months symptomatic with 2 or more of following; oral thrush, +/- severe pneumonia,+/- severe wasting/malnutrition, +/-severe sepsis, severe immunosuppression should be suspected and ARV treatment is indicated

CD4 values where available may be used to guide decision making, CD4% below 25 requires ARV treatment

Other factors that support diagnosis of clinical stage 4 HIV infection in an HIV seropositive infant are recent maternal death or advanced HIV disease in mother.

Confirmation of the diagnosis of HIV infection should be sought as soon as is possible

Explanatory Notes

The clinical staging system for infants and children is designed to:

1. Be used where HIV infection is confirmed by HIV antibody testing in children over 18 months of age, virological or P24 Antigen testing in those < 18 months of age.

2. Provide greater consistency between adult and pediatric staging and harmonize with HIV/AIDS surveillance definitions.

3. Classify disease in a progressive sequence from least to most severe, with each higher clinical stage having a poorer prognosis. Once a stage 3 clinical event has occurred, the prognosis remains that of stage 3 and does not improve, even with resolution of the original condition.

4. Provide simple guidance to assist clinical care providers in when to start, substitute, switch or stop ARV therapy in HIV infected infants and children, or trigger referral as outlined in WHO ART guidelines for a public health approach.

5. Be largely used with reference to CURRENT clinical events, meaning clinical events that have been diagnosed or are being managed at this episode.

6. Be considered in relation to previous clinical events, such as reported TB, severe pneumonia, PCP or other conditions. This is RETROSPECTIVE clinical staging and requires caution. **Note:** Reported history of a stage 3 or stage 4 clinical event should have immediate assessment by, or referral to, HIV care providers able to initiate ARV treatment.
7. Be used to guide clinicians in assessing the response to ARV treatment, particularly where viral load and or CD4 counts/or percent are not widely or easily available. However further evidence is required to determine the significance of staging events once on ART.

New or recurrent stage 4 events may suggest failure of response to treatment,
New or recurrent stage 2 or 3 events may suggest inadequate response to treatment, potentially due to poor adherence.

Note: Clinical events in the first 3 months of starting ART may be due to immune restoration disease (IRD) not a poor response to ART. This is reported less commonly in children.
Note: Total lymphocyte count (TLC) is not currently recommended for monitoring therapy.

8. Encourage clinical care providers to consider diagnostic testing for HIV for infants and children with the clinical events suggestive of HIV disease. Stage 3 or 4 events should prompt the offer of HIV diagnostic testing.

Appendix 5: Adverse events grading toxicity

	Diagnosis	Tested by	1 mild	2 moderate	3 severe	4 very severe
General	Headache	Interview	Transient or mild discomfort; no limitation in activity; no medical intervention/therapy required.	Mild to moderate limitation in activity; some assistance may be needed; no or minimal medical intervention/therapy required	Marked limitation in activity; some assistance usually required; hospitalization possible	Extreme limitation in activity; significant assistance required; significant medical intervention/therapy required; hospitalization probable
	Asthenia (weakness/fatigue)	Interview	Transient or mild discomfort; no limitation in activity; no medical intervention/therapy required.	Mild to moderate limitation in activity; some assistance may be needed; no or minimal medical intervention/therapy required	Marked limitation in activity; some assistance usually required; hospitalization possible	Extreme limitation in activity; significant assistance required; significant medical intervention/therapy required; hospitalization probable
	Neuro-psych/mood	Interview	Mild confusion, abnormal dreams, impaired concentration, agitation. Interferes with normal activity < 25%	Moderate confusion, abnormal dreams, impaired concentration, or agitation that interferes with normal activity 25 – 50% or	Severe confusion, abnormal thinking, amnesia, depersonalization, hallucinations that interfere with normal activity > 50%	Very severe confusion, abnormal thinking, amnesia, depersonalization, hallucinations that render a person unable to care for self.

Cutaneous	Rash	Interview For symptoms of pruritus	Mild pruritus or rash over < 50% of body	Mode rate pruritus or over >50% of body	Severe pruritus or painful lesions	Very severe pruritus or painful lesions
		Physical Exam	Erythema	Diffuse maculopapular rash or dry desquamation	Vesiculation or moist desquamation or ulceration	Any one of the following: mucous membrane involvement, suspected SJS or TEN, erythema multiforme, necrosis requiring surgery, exfoliative dermatitis
Gastrointestinal	Nausea	Interview	Transient; reasonable oral intake maintained	Oral intake decreased <3 days	Minimal oral intake for ≥ 3 days	Unable to tolerate any oral intake for ≥ 3 days
	Vomiting	Interview	Transient: 2-3 episodes per day or lasting < 1 week	Persistent: 4-5 episodes per day or lasting ≥ 1 week	Vomiting of all food/fluids in 24 hours	Vomiting of all food/fluids for > 1 day
	Diarrhea	Interview	Mild or transient: 3-4 loose stools per day or mild diarrhea lasting < 1 week	Moderate or persistent: 5-7 loose stools per day or diarrhea lasting ≥ 1 week	>7 loose stools per day or bloody diarrhea	Very severe diarrhea resulting in hypotensive shock

Neurologic	Peripheral neuropathy	Interview for paresthesia (burning, tingling)	Mild: intermittent, does not interfere with ambulation	Moderate: continuous, minimal interference with ambulation	Severe: continuous, painful, moderate interference with ambulation	Incapacitating: very painful, substantially interferes with ambulation
		Physical exam for Neuro-motor	Mild weakness in muscles of feet, but able to walk and/or mild increase or decrease in reflexes	Moderate weakness in feet, unable to walk on heels and/or toes, mild weakness in hands. Still able to do most hand tasks and/or loss of previously present reflex or development of hyperreflexia and/or unable to do deep knee bends due to weakness	Marked distal weakness (unable to dorsiflex toes or foot drop), and moderate proximal weakness (in hands interfering with ADLs and/or requiring assistance to walk and/or unable to rise from chair unassisted)	Confined to bed or wheelchair because of muscle weakness
		Physical exam for Neuro-sensory	Mild impairment (decrease sensation to vibration, pinprick, temperature in great toes) in focal area or symmetrical distribution	Moderate impairment (moderate decrease in sensations to vibration, pinprick, temperature to ankles) and/or joint position or mild impairment that is not symmetrical	Severe impairment (decrease or loss of sensation to knees or wrist) or loss of sensation of at least a moderate degree in multiple different body areas (ex upper and lower extremities)	Sensory loss involves limbs and trunk

Hematologic	Anemia	Hemoglobin (g/dL)	8.0 – 9.0	7.0 – 7.9	6.5 – 6.9	< 6.5
	Neutropenia	Absolute neutrophil count (#/mm^3)	1000 – 1500	750 – 999	500 –749	<500
	Leukopenia (if determination of absolute neutrophil is not available)	Absolute leukocyte count (#/mm^3)	1500 – 2500	1000 – 1499	750 – 999	<750
	Thrombocytopenia	Platelet count (#/mm^3)	75,000 – 99,000	50,000 – 74,999	20,000 – 49,999	<20,000
Organ toxicity	Pancreatic toxicity	Any of: Amylase Pancreatic amylase Lipase	>1.0 – 1.5 ULN	>1.5 – 2.0 ULN	>2.0 – 5.0 ULN	>5.0 ULN
	Hepatotoxicity	Any of: AST (SGOT) ALT (SGPT) GGT Alkaline phosphatase	>1.25 – 2.5 ULN	>2.5 – 5.0 ULN	>5.0 – 10.0 ULN	>10.0 ULN
Endocrinologic	Hyperglycemia	Glucose (mg/dL) [Non-fasting and no prior diabetes]	116 – 160	161 – 250	251 – 500	>500
Lipid	Hypertriglyceridemia	Triglycerides (mg/dL)		400 – 750	751 – 1200	>1200
	Hypercholesterolemia	Cholesterol (mg/dL) [total cholesterol]	200 – 239	240 – 300	300 – 400	> 400

Adapted from Division of AIDS table for Grading Severity of Adult Adverse Experiences, August 2001 Division of AIDS, National Institute for Allergy and infectious Diseases, National Institutes of Health, USA

[i] Acute retroviral syndrome : Acute febrile illness 2-4 wks post-exposure often with lymphadenopathy and skin manifestations, pharyngitis.

[2] TB may occur at any CD4 count, and this must be considered where available. If CD4 is less than 200 it should be considered as a stage 4 event. Diagnosis and treatment of both pulmonary and extrapulmonary TB should be in line with international and national guidelines.

[ii] Moderate malnutrition: Defined as very low weight for age - up to - 2SD for age http://www.who.int/child-adolescent-health/publications/CHILD_HEALTH/WHO_FCH_CAH_00.1.htm or page4 http://www.who.int/nut/documents/manage_severe_malnutrition_eng.pdf

[iii] As for footnote 2. TB is particularly difficult to diagnose in infants and young children.

[iv] Severe Malnutrition: Defined as : visible severe wasting or oedema of both feet and weight for height of -3SD Ref: http://www.who.int/child-adolescent-health/publications/CHILD_HEALTH/WHO_FCH_CAH_00.1.htm