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The Use of Antiretroviral Therapy: A Simplified Approach for Resource-Constrained Countries

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FOREWORD

Highly active antiretroviral treatment (ART) has decreased morbidity and mortality of people living with HIV/AIDS in Australia, Europe and Northern America. However the vast majority of the 40 million people living with HIV/AIDS in developing countries do not have access to comprehensive HIV/AIDS care and to antiretroviral treatment in particular. WHO conservatively estimates that in 2002, some 6 million people in developing countries are in need of ART. However, only 230,000 have access to ART, and half of these live in Brazil.

Health care providers in the public and private sector and policy makers face an increasing demand for ART of people affected. Antiretroviral medicines are available in the private sector. However treatment guidelines and services to administer ART are lacking and health care providers have often not received adequate training in comprehensive HIV/AIDS care including the administration of ART in many countries of the region.

To respond to this situation, the WHO South-East Asia Regional Office has developed guidelines for The Use of Antiretroviral Therapy: A Simplified Approach for Resource-Constrained Countries and Fact Sheets on Antiretroviral Drugs. There are wide variations among member countries in the availability of resources and health infrastructures. It is hoped that these guidelines will provide a model to assist countries in the region to formulate national antiretroviral treatment guidelines according to their own needs and resources.

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ABBREVIATIONS

3TC	Lamivudine
ABC	Abacavir
AIDS	Acquired immune deficiency syndrome
ALT	Alanine transaminase
ARV	Antiretroviral
ART	Antiretroviral therapy
AST	Aspartate transaminase
AZT	Azidothymidine (Zidovudine)
BHIVA	British HIV Association
CBC	Complete blood count
CD4	CD4+ T Lymphocyte
d4T	Stavudine
ddI	Didanosine
DHHS	Department of Health and Human Services of USA
DOT	Directly observed therapy
DOTS	Directly observed therapy, short-course
EFZ	Efavirenz
HIV	Human immunodeficiency virus
IDV	Indinavir
LPV	Lopinavir
LPV/r	Lopinavir/ritonavir
MTCT	Mother-to-child transmission of HIV
NFV	Nelfinavir
NNRTI	Non-nucleoside reverse transcriptase inhibitor
NsRTI	Nucleoside analog reverse transcriptase inhibitor
NtRTI	Nucleotide analog reverse transcriptase inhibitor
NVP	Nevirapine
OI	Opportunistic infection
PCP	*Pneumocystis carinii* pneumonia
PI	Protease inhibitor
PLHA	People living with HIV/AIDS
PMTCT	Prevention of Mother-to-Child Transmission of HIV

RTV	Ritonavir
r	Low dose ritonavir boost
SQV	Saquinavir
STI	Sexually transmitted infection
TB	Tuberculosis
TDF	Tenofovir disoproxil fumarate
TLC	Total lymphocyte count
VCT	HIV voluntary counseling and testing
WHO	World Health Organization
ZDV	Zidovudine

1. INTRODUCTION

The Acquired Immunodeficiency Syndrome (AIDS) was first reported in the *Morbidity and Mortality Weekly Report* as "*Pneumocystis* pneumonia - Los Angeles,"[1] in 1981. Since then, AIDS has become the most devastating disease that mankind has ever faced.

Since the epidemic began, more than 60 million people have been infected with the human immunodeficiency virus (HIV). By the end of 2001 an estimated 40 million people globally were living with HIV with about one-third aged between 15-24 years. Ninety-five percent of new infections are occurring in developing countries and almost 50% are women. [2]

HIV/AIDS was late in coming to Asia. Until the late 1980s, no country in the region had experienced a major epidemic and, in 1999, only Cambodia, Myanmar and Thailand had documented significant nationwide epidemics. This situation is now rapidly changing. In 2001, 1.07 million adults and children were newly infected with HIV in Asia and the Pacific bringing to a total of 7.1 million people living with HIV/AIDS in this region. Of particular concern are the marked increases registered in some of the world's most heavily populated countries. At the end of 2001, the national adult HIV prevalence rate in India was under 1%, with an estimated 3.97 million Indians living with HIV/AIDS. India ranks second after South Africa in the number of people living with HIV/AIDS. In Indonesia and Nepal there are concentrated epidemics in high-risk groups such as injecting drug users (IDU). In Bangladesh, Bhutan, Maldives and Sri Lanka infection rates are low, though risk behaviour is common.[3] TB is the leading opportunistic infection in HIV-positive persons. HIV fuels the TB epidemic and is a particular threat to Asia and the Pacific, which bears more than 60% of the World's TB burden.

Early, large-scale and focused prevention programmes can reduce infection rates in high-risk groups and the risk of spread of HIV among the wider population. An excellent example is Thailand, where prevention efforts have probably averted millions of HIV infections.[4] Cambodia is another

example where preventive measures have been effective. Strategies to prevent HIV transmission should remain a priority in combating HIV/AIDS.

Antiretroviral treatment for HIV infected patients was first introduced in 1986. Zidovudine (ZDV), a nucleoside reverse transcriptase inhibitor (NsRTI), was the first drug that was used and was shown to reduce deaths and accompanying opportunistic infections in patients with advanced HIV infection.[5] Over the next few years other NsRTIs like didanosine (ddI), lamivudine (3TC), and stavudine (d4T) were introduced. However, the benefits of single drug therapy were short-lived due to the emergence of resistance. Subsequently, it was shown that combining 2 or 3 antiretroviral (ARV) drugs produced more sustained benefit. New classes of drugs, the protease inhibitors (PI) and non-nucleoside reverse transcriptase inhibitors (NNRTI) permitted the use of more potent antiretroviral regimens. These regimens, consisting of three or more drugs, have resulted in dramatic reduction in HIV levels in blood and markedly improved immune function. In developed countries treatment of HIV infection using regimens of 3 or more antiretroviral drugs has been recommended.[6,7]

In Europe and North America, AIDS mortality has dropped significantly in large part due to access to regimens of 3 or more antiretroviral drugs.[8-10] Patients receiving these regimens are less likely to develop opportunistic infections including TB and require less admissions to hospital than patients with untreated disease.[11,12] Combination antiretroviral therapy (ART) leads to reduction in plasma HIV RNA level (viral load) and rise in CD4 counts with at least partial restoration of immune function.[13-15] Combination therapy also significantly slows the progression of HIV-1 disease.[13] Furthermore, studies indicate that low viral load is associated with lower risk of heterosexual and perinatal transmission.[16,17] Although combination of three antiretroviral drugs is expensive, studies indicate that it is a cost effective use of resources in the developed world.[18,19] Since the advent of combination antiretroviral therapy, the disease has been transformed into a treatable and chronic condition for a significant proportion of those with access to this treatment. Appropriate treatment can prevent not only infected individuals from succumbing to life-threatening illness from AIDS, but may play a major role in prevention by reducing viral load of those under treatment and by encouraging greater participation in prevention programmes.

Millions of people in developing countries infected with HIV face disease and early death unless they receive appropriate life-extending medical care. WHO conservatively estimates that in 2002, some 6 million in developing countries are in need of antiretroviral therapy. However, only 270,000 have access to them, and half of these live in Brazil. The United Nations General Assembly Special Session on HIV/AIDS (UNGASS) in 2001 advocated for the complementarity of HIV care and prevention and urged governments to provide the highest attainable standard of care, including antiretroviral treatment to people living with HIV/AIDS.

The main obstacles to the use of antiretroviral drugs in developing countries have been the high cost and the lack of health infrastructure necessary to use them. Also, there are concerns that difficulties with adherence to complicated medication regimens would promote and spread drug resistance.[20] However, it is time to look more seriously at antiretroviral treatment as a part of comprehensive care for people living with HIV/AIDS. The delivery of effective care and antiretroviral treatment for people living with HIV/AIDS in poorest countries is an urgent priority and should complement programmes to prevent HIV transmission. The reasons for combining AIDS prevention and care include a humanitarian rationale, to save children and the fabric of society, for continuing economic development and to optimize preventive efforts. When testing is linked to care, people have an incentive to be tested providing a rational response: primary prevention for HIV negative persons and comprehensive care for HIV-positive patients.[21]

Brazil and Thailand have demonstrated that it is possible to deliver ART in a mid-income developing country. Data from Brazil show that HIV associated morbidity and mortality, in particular TB incidence and hospitalization time were markedly reduced through the introduction of ART (Vitoria M, Ministry of Health Brazil, Second Global TB/HIV Working Group Meeting, Durban, South Africa, 14-16 June 2002). In a study in Haiti, directly observed therapy (DOT) was used for the administration of ART with considerable success.[22]

Some of the pharmaceutical companies in developing countries produce generic drugs at a fraction of the cost in developed countries, making it possible for these drugs to be made available for therapy in resource poor settings.[23] These guidelines on the appropriate and rationale use of ART are relevant because these drugs are now available in developing countries,

although mostly in the private sector and patients are using them. There is a growing international consensus and pressure that treatment of people living with HIV/AIDS with combination antiretroviral therapy in developing countries is possible. On the basis of clinical data, both, from developed and developing countries, there is evidence that AIDS treatment results in significant gains in extending duration and quality of life.

The guidelines are primarily intended for:

(1) Physicians and other health care providers

(2) National AIDS programme managers and other health planners involved in national HIV care and treatment programmes as a reference for national treatment guidelines.

The guidelines will require updating at regular intervals as new significant data emerge.

2. DOCUMENT OBJECTIVES

The objectives of WHO guidelines are:

(1) to provide a standard approach for the use of antiretroviral treatment (ART) as part of comprehensive HIV/AIDS care;

(2) to be a source of reference for physicians and other healthcare providers caring for patients with HIV/AIDS as well as AIDS programme managers and health planners involved in national HIV care and treatment programmes, and

(3) to be a source of reference for people living with HIV/AIDS.

This document contains recommendations for the use of antiretroviral drugs for the treatment of adults and adolescents $\geq$ 13 years of age particularly in countries of the WHO South-East Asia Region.

3. PRINCIPLES OF HIV THERAPY

The goals of antiretroviral therapy are:

- reduction of HIV related morbidity and mortality

- improvement of quality of life
- restoration and/or preservation of immunological function
- maximal and durable suppression of viral replication.

The following general principles apply for the clinical use of ART:

(1) A continuous high level of replication of HIV takes place from the early stages of infection. At least 10^{10} particles are produced and destroyed each day.[24] Despite this high level of viral replication, most patients remain well for many years without any antiretroviral therapy.

(2) Ongoing HIV replication leads to progressive immune system damage resulting in susceptibility to opportunistic infections (OI), malignancies, neurological diseases, wasting and, ultimately, death.

(3) Plasma HIV RNA levels indicate the magnitude of HIV replication and the associated rate of CD4+ T cell destruction, whereas CD4+ T cell counts indicate the extent of HIV induced immune damage.

(4) Measured concentration of viral load is predictive of the subsequent risk of disease progression and death. Regular measurements of CD4+T cell and plasma HIV RNA levels (if possible to perform) are necessary to determine the risk of disease progression in HIV infected patients and to determine when to initiate or modify ART regimens.

(5) Rates of disease progression differ among HIV infected persons. Treatment decisions should be individualized by CD4+ T cell counts and by plasma HIV RNA levels (where it is possible to perform)

(6) Combination antiretroviral therapy to suppress HIV replication to below the levels of detection of sensitive plasma HIV RNA assays limits the potential for selection of antiretroviral resistant HIV variants and delay disease progression. Therefore, maximum achievable suppression of HIV should be a goal of therapy.

(7) The most effective means to establish durable suppression of HIV replication is the simultaneous initiation of a combination of effective anti-HIV drugs with which the patient has not been

previously treated and that are not cross-resistant with ARV drugs with which the patient has been previously treated.

(8) Antiretroviral drugs used in combination therapy regimens should be used according to optimum schedules and dosages. ARV drugs are limited in number and mechanism of action, and cross resistance between specific drugs has been documented. Change in ART increases future therapeutic constraints.

(9) Women should receive optimal antiretroviral therapy regardless of pregnancy status.

(10) The same principles of ART apply to HIV infected children, adolescents and adults, although the treatment of HIV infected children involves special considerations.

(11) HIV infected persons, even those whose viral loads are below detectable limits, should be considered infectious. Therefore, they should be counselled to avoid sexual and drug use behaviours that are associated with either transmission or acquisition of HIV and other infectious pathogens.[25]

4. STARTING ANTIRETROVIRAL THERAPY

4.1 Prerequisites

It is most desirable to have specific services and facilities before starting ART due to the complexity of the therapy, the need for monitoring and the cost of therapy.

These services include:

(1) Access to HIV voluntary counseling and testing (VCT) and institution of follow up counseling services to identify those who could benefit from the programme to ensure continued psychosocial support and to enhance adherence to treatment. VCT is useful to identify HIV infected people.

(2) Medical services capable of identifying and treating common HIV-related illnesses and opportunistic infections.

(3) Reliable laboratory services capable of doing routine laboratory investigations such as complete blood count and chemistry. Access to a referral laboratory capable of doing CD4+T lymphocyte count is desirable to monitor therapy.

(4) Reliable and affordable access to quality antiretroviral drugs, and drugs to treat opportunistic infections and other related illness.

4.2 Clinical Evaluation

Prior to starting therapy patients should have the following evaluation performed:

- Complete history and physical examination
- Routine laboratory investigations
- CD4+T lymphocyte count/ total lymphocyte count (TLC)

A detailed clinical evaluation is essential prior to initiating antiretroviral therapy and should aim to:

- Assess the clinical stage of HIV infection
- Identify past HIV-related illnesses
- Identify current HIV-related illnesses that would require treatment
- Identify co-existing medical conditions and treatments that may influence the choice of therapy

History and Physical Examination

A medical history should include questions on the following:

- when and where was the diagnosis of HIV made
- what is this person's possible source of HIV infection
- what are the current symptoms and concerns of the patient
- past medical history of symptoms, known diagnoses and treatments given

- history of symptoms of or previous treatment for tuberculosis
- history of possible contact with tuberculosis
- history of possible sexually transmitted infections
- history of pregnancy
- history of previous antiretroviral therapy
- history of medication and oral contraceptive use in women
- social habits and sexual history

The physical examination should include the following points:

- patient's weight
- skin: herpes zoster, Kaposi's sarcoma, HIV dermatitis
- lymphadenopathy
- oropharyngeal mucosa: candidiasis, Kaposi's sarcoma, hairy leucoplakia
- examination of heart and lungs
- examination of abdomen particularly for liver and spleen enlargement
- examination of neurological and musculoskeletal system: mental state, motor and sensory deficit
- examination of optic fundus: retinitis and papilloedema
- examination of the genital tract/gynaecological examination

Laboratory Investigations

Essential

- HIV serology
- CD4+T lymphocyte counts (if available) or total lymphocyte count (TLC)
- Complete blood count and chemistry profile
- Pregnancy test

Supplementary tests indicated by history and physical examination

- Chest x-ray
- Urine for routine and microscopic examination
- Hepatitis C virus (HCV) and hepatitis B virus (HBV) serology (depending on test availability and resources)

It is most important to confirm the diagnosis of HIV infection by tests performed by a trained technician, preferably in a diagnostic laboratory. The test results should include the type of test performed to establish the diagnosis based on WHO guidelines. In case there is any doubt, the tests should be repeated in a standard/referral laboratory.

The blood chemistry profile should, if possible, include serum creatinine and/or blood urea to assess baseline renal function, serum glucose, and serum alanine or aspartate aminotransferase to assess the possibility of hepatitis and to monitor drug toxicity. Other tests that may be performed include serum bilirubin, serum lipids and serum amylase.

4.3 Indications

With currently available antiretroviral agents, eradication of HIV infection is not likely. This is largely due to the establishment of a pool of latently infected CD4+T lymphocytes during the very early stage of acute HIV infection that persists with an extremely long half-life, even with prolonged suppression of plasma viraemia to <50 copies/mL.[26-28] The decay half-life of resting memory CD4 lymphocytes with latent HIV provirus is calculated to be at least 6 months and as long as 44 months. Thus, HIV eradication with ART alone would take a decade or more and is not a realistic goal.[28,29]

The aim of treatment is thus to prolong and improve the quality of life by maintaining maximal suppression of virus replication for as long as possible. Reductions in plasma viraemia achieved with antiretroviral therapy account for much of the clinical benefits associated with ART[30].

Table 1. *Recommendations for initiating antiretroviral therapy in adults and adolescents with documented HIV infection*[31,32]

If CD4 testing available:
– WHO Stage IV disease irrespective of CD4 cell count [(a)]
– WHO Stage I, II or III [(a)] with CD4 cell counts < 200/mm^3 [(b)]
If CD4 testing unavailable:
– WHO Stage IV disease irrespective of total lymphocyte count
– WHO Stage II or III disease with a total lymphocyte count 1200/mm^3 [(c)]

[(a)] Treatment is also recommended for patients with advanced WHO Stage III disease including recurrent or persistent oral thrush and recurrent invasive bacterial infections irrespective of CD4 cell or total lymphocyte count.

[(b)] A CD4 level of 200/mm^3 corresponds to a CD4 percentage of approximately 15%. The precise CD4 level above 200/mm^3 at which to start ARV treatment has not been established but the presence of symptoms and the rate of CD4 cell decline (if measurement possible) should be factored into the decision making.

[(c)] A total lymphocyte count of 1200/mm^3 can be substituted for the CD4 count when the latter is unavailable and HIV-related symptoms exist. It is less useful in the asymptomatic patient. Thus, in the absence of CD4 cell testing, asymptomatic HIV infected patients (WHO Stage I) should not be treated because there is currently no other reliable marker available in severely resource-constrained settings.

For WHO staging system for HIV infection[32] and CDC classification system for HIV infection,[33] please see annexes I and II.

Antiretroviral drugs may also be used for post-exposure prophylaxis (PEP) following accidental occupational and possible sexual or other non-occupational exposure to HIV.[34,35]

Antiretroviral drugs are used for prevention of mother to child transmission of HIV, which is beyond the scope of this document.

Important considerations for starting therapy also include medium/long term availability and affordability of drugs by the patient or the programme.

Asymptomatic HIV Infection

Therapy is recommended for **asymptomatic** patients (WHO Adult Stage I disease) when CD4 count nears or falls below **200 cells/mm^3**.[6,7,31,32] Randomised clinical trials provide strong evidence for treating patients with **<200 cells/mm^3 CD4 count**.[13,14,36]

CD4 count of 200/mm^3 corresponds to CD4 percentage of 15%. The CD4 percentage may be used as an alternate to the CD4 count/mm^3.

The optimal time to start ART for **asymptomatic** patients with CD4+T cell counts >200/mm^3 is not known.[37,38] Recommendation for therapy in this group should be based on patient's wishes for therapy, the CD4 count, and the rate of decline of CD4 count.

In **asymptomatic** patients with **CD4+ T cell count > 350/mm^3**, therapy should be deferred.[6,7]

Symptomatic HIV Infection

Antiretroviral therapy is recommended for patients with symptomatic disease (AIDS, WHO Adult Stage IV and advanced Stage III) irrespective of the CD4 cell count or total lymphocyte count. Therapy is also recommended for WHO Adult Stages II and III patients when CD4 count is less than 200 cells/mm^3 or a CD4 percentage of <15%. If CD4 cell count monitoring is unavailable, treatment is recommended for symptomatic patients (WHO Adult Stage II and III disease) with total lymphocyte counts below 1200/mm^3. In symptomatic patients, the total lymphocyte count in combination with clinical staging is a useful marker of prognosis and survival. However, in asymptomatic HIV infected individuals, total lymphocyte count is less useful.

Treatment of tuberculosis and other serious opportunistic infections may be more important than antiretroviral therapy. In the event of possible drug interactions, it may be necessary to postpone antiretroviral therapy until the opportunistic infection is adequately controlled.

Plasma HIV RNA level strongly predicts the rate of decrease in CD4+ lymphocyte count and progression to AIDS and death, but the prognosis of HIV-infected persons is more accurately defined by combined measurement of plasma HIV-1 RNA and CD4+ lymphocytes.[39] The HIV viral load is a strong predictor of clinical outcome in the mid- and long-term period but the

immediate risk of opportunistic complications of HIV-1 disease is better dictated by the CD4 cell count. ***However, in resource-limited settings, an assessment of viral load (using HIV-1 RNA levels) is not considered essential to start therapy.***

5. ANTIRETROVIRAL DRUGS RECOMMENDED FOR USE

5.1 Drugs and Doses

Twelve antiretroviral drugs have been included in the **WHO Model List of Essential Medicines** in April 2002 and are as follows:

Table 2. *Antiretroviral drugs*

Nucleoside reverse transcriptase inhibitors (NsRTI)	
Abacavir (ABC)	tablet 300 mg, oral solution 100 mg/5 ml
Didanosine (ddI)	tablet 25 mg, 100 mg, 150 mg, 200 mg
Lamivudine (3TC)	tablet 150 mg, oral solution 50 mg/5 ml
Stavudine (d4T)	capsule 15 mg, 20 mg, 30 mg, 40 mg, oral solution 5 mg/ml
Zidovudine (ZDV or AZT)	capsule 100 mg, 250 mg, 300 mg; injection 10 mg/ml in 20 ml vial; oral solution 50 mg/5 ml
Non nucleoside reverse transcriptase inhibitors (NNRTI)	
Efavirenz (EFV or EFZ)	capsule 50 mg, 100 mg, 200 mg
Nevirapine (NVP)	tablet 200 mg, oral suspension 50 mg/5 ml
Protease inhibitors	
Indinavir (IDV)	capsule 100 mg, 200 mg, 333 mg, 400 mg
Ritonavir (RTV, r) [a]	capsule 100 mg, oral solution 400 mg/5 ml
Lopinavir + ritonavir (LPV/r)	capsule 133.3 mg + 33 mg, oral solution 400 mg/5 ml + 100 mg/5 ml
Nelfinavir (NFV)	tablet 250 mg, powder 50 mg/g
Saquinavir (SQV)	capsule gel filled 200 mg

[a] Ritonavir is recommended for use in combination with indinavir, lopinavir and saquinavir as a booster and not as a drug in its own right.

Doses and common side effects are listed in tables 3-7.

5.2 Side Effects

NsRTIs

Drugs belonging to the class of NsRTIs are associated with hepatic steatosis and lactic acidosis due to cellular mitochondrial toxicity. Lactic acidosis may initially present with nonspecific gastrointestinal symptoms of nausea, vomiting, abdominal pain and distension, generalised weakness. This may progress to tachypnoea and dyspnoea and eventually respiratory failure. Serum lactate levels may be elevated. NsRTI should be stopped if lactic acidosis is suspected. Approximately 3-5% of adults and children receiving ***abacavir*** develop a potentially ***fatal hypersensitivity reaction***.[40] Symptoms include fever, gastrointestinal complaints (nausea, vomiting, diarrhoea, or abdominal pain), fatigue and/or respiratory symptoms (pharyngitis, cough, or dyspnoea). Physical findings may include lymphadenopathy, ulceration of mucous membranes and skin rash. Laboratory abnormalities may include elevated liver enzymes, creatinine phosphokinase, creatinine and thrombocytopenia. Abacavir should be stopped immediately if hypersensitivity reaction is suspected and should never be restarted since deaths have occurred within hours of rechallenge.

NNRTIs

Drugs belonging to the class of NNRTIs are associated with skin rash that may be mild or progress to Stevens-Johnson syndrome. NNRTI may also cause serum alanine/aspartate aminotransferase elevation and rare fatal cases of hepatitis. Among the NNRTIs, *nevirapine* most frequently causes clinical hepatitis. Approximately two thirds of nevirapine associated clinical hepatitis occur within the first 12 weeks; it may rapidly progress to fulminant hepatic failure**. *Nevirapine must be given 200 mg once daily for 2 weeks and then increased to 200 mg twice daily to reduce the incidence of hepatotoxicity.*** Close monitoring of clinical symptoms and serum transaminases are recommended after starting nevirapine therapy, initially every 2 weeks for the first month, then monthly for 12 weeks and every one to three months thereafter. Patients who develop hepatic toxicity while treated with nevirapine should not be restarted on that drug. **Efavirenz** is considered to be teratogenic and should be avoided in pregnancy. Efavirenz has also adverse effects on central nervous system.

PIs

The class specific side effects of **protease inhibitors** include insulin resistance, diabetes mellitus, hyperlipidemia, lipodystrophy, hepatitis, bone disorders, and increased bleeding in haemophiliacs.

When patients are receiving ART, it is appropriate to routinely monitor complete blood count, serum alanine or aspartate aminotransferase, serum glucose and serum creatinine and/or blood urea, if possible, every 3-6 months. Other tests such as serum amylase and serum lipid may be performed, if indicated. Such testing will help to detect adverse drug effects so that therapy may be modified, if necessary.

Table 3. *Nucleoside Reverse Transcriptase Inhibitors (NsRTI)*[32,41,42]

Generic name	Dose	Adverse effects
Abacavir (ABC)	300 mg twice daily or with ZDV and 3TC (Trizivir®) 1 tablet twice daily Trizivir® contains 300 mg ZDV, 150 mg 3TC, and 300 mg ABC	Hypersensitivity reaction **(can be fatal)** Fever, rash, fatigue Nausea, vomiting, anorexia Respiratory symptoms (sore throat, cough) Lactic acidosis with hepatic steatosis (rare)
Didanosine (ddI)	>60 kg: 200 mg twice daily or 400 mg once daily <60 kg: 125 mg twice daily or 250 mg once daily	Pancreatitis Peripheral neuropathy Nausea, diarrhoea Lactic acidosis with hepatic steatosis (rare)
Lamivudine (3TC)	150 mg twice daily <50 kg: 2 mg/kg bid	Minimal toxicity Lactic acidosis with hepatic steatosis (rare)
Stavudine (d4T)	>60 kg: 40 mg twice daily <60 kg: 30 mg twice daily	Pancreatitis Peripheral neuropathy Lactic acidosis with hepatic steatosis (rare) Lipoatrophy
Zidovudine (ZDV, AZT)	300 mg twice daily 250 mg twice daily (alternative dose) ZDV/3TC combination 300 mg/150 mg twice daily	Anaemia, neutropenia, Gastrointestinal intolerance, Headache, insomnia, myopathy Lactic acidosis with hepatic steatosis (rare)

Table 4. *Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTI)*[32,41,42]

Generic name	Dose	Adverse effects
Nevirapine (NVP)	200 mg once daily for 14 days followed by 200 mg twice daily	Skin rash, Stevens-Johnson syndrome Elevated serum aminotransferase levels Hepatitis, **life-threatening** hepatic toxicity
Efavirenz (EFV)	600 mg once daily (bed time administration is suggested to decrease CNS side effects)	CNS symptoms: dizziness, somnolence, insomnia, confusion, hallucinations, agitation Elevated transaminase levels Skin rash

Table 5*. Protease Inhibitors (PI)*[32]

Generic name	Dose
Nelfinavir (NFV)	1250 mg twice daily
Indinavir/ritonavir (IDV/r)	800 mg/100 mg twice daily [a, c]
Lopinavir/ritonavir (LPV/r)	400 mg/100 mg twice daily (533 mg/133 mg twice daily when combined with EFZ or NVP)
Saquinavir/ ritonavir (SQV/r)	1000/100 mg twice daily [b, c]

[a] This dosage regimen is not approved but supportive data exist and the regimen is in common clinical use.

[b] This dosage regimen is not approved but supportive data exist for its use. Both the hard-gel and soft-gel capsule formulations can be used when SQV is combined with RTV.

[c] Dosage adjustment when combined with an NNRTI is indicated but a formal recommendation cannot be made at this time. One consideration is to increase the RTV component to 200 mg bid when EFZ or NVP is used concomitantly. More drug interaction data are needed.

Table 6. *Protease Inhibitors* [41,42]

Generic name	Adverse effects
Indinavir (IDV)	Nephrolithiasis, gastrointestinal intolerance, *hyperglycaemia, fat redistribution and lipid abnormalities*, headache, dizziness, rash, thrombocytopenia, alopecia, bleeding in haemophilia patients
Ritonavir (RTV)	Gastrointestinal intolerance, nausea, vomiting, paresthesia, hepatitis and pancreatitis, *hyperglycaemia, fat redistribution and lipid abnormalities*
Lopinavir + ritonavir (LPV/r)	GI intolerance, nausea, vomiting, elevated transaminase enzymes, *hyperglycaemia, fat redistribution and lipid abnormalities*
Nelfinavir (NFV)	Diarrhoea, *hyperglycaemia, fat redistribution and lipid abnormalities*
Saquinavir (SQV)	Gastrointestinal intolerance, nausea, vomiting, headache, elevated transaminase enzymes, *hyperglycaemia, fat redistribution and lipid abnormalities*

The doses listed are those for individuals with normal renal and hepatic function. Product specific information should be referred to for dose adjustments that may be indicated with renal or hepatic dysfunction or for potential drug interactions with other HIV and non-HIV medications.

Table 7. *Clinical signs, symptoms, monitoring and management of symptoms of serious adverse effects of antiretroviral drugs that require drug discontinuation*[32]

Adverse Effect	Possible offending drug/s	Clinical signs / symptoms	Management
Acute hepatitis	Nevirapine (NVP); EFV less common; more uncommon with zidovudine (ZDV), didanosine (ddI), stavudine (d4T) (<1%); and protease inhibitors (PI), most frequently with ritonavir (RTV)	Jaundice, liver enlargement, gastrointestinal symptoms, fatigue, anorexia; NVP-associated hepatitis may have hypersensitivity component (drug rash, systemic symptoms, eosinophilia)	If possible, monitor serum transaminases, bilirubin. All ARV should be stopped until symptoms resolve. NVP should be permanently discontinued.

Adverse Effect	Possible offending drug/s	Clinical signs / symptoms	Management
Acute pancreatitis	ddI, d4T; lamivudine (3TC) (infrequent)	Nausea, vomiting, and abdominal pain	If possible, monitor serum pancreatic amylase, lipase. All ART should be stopped until symptoms resolve. Restart ART with change to different NRTI, preferably one without pancreatic toxicity (e.g., ZDV, ABC).
Lactic acidosis	All nucleoside analogue reverse transcriptase inhibitors (NsRTIs)	Initial symptoms are variable: a clinical prodromal syndrome may include generalized fatigue and weakness, gastrointestinal symptoms (nausea, vomiting, diarrhoea, abdominal pain, hepatomegaly, anorexia, and/or sudden unexplained weight loss), respiratory symptoms (tachypnea and dyspnea) or neurologic symptoms (including motor weakness).	Discontinue all ARV; symptoms may continue or worsen after discontinuation of ART. Supportive therapy. Regimens that can be considered for restarting ART include a PI combined with an NNRTI and possibly either ABC or TDF.
Hyper-sensitivity reaction	Abacavir (ABC) Nevirapine (NVP)	ABC: Constellation of acute onset of symptoms including: fever, fatigue, myalgia, nausea/vomiting, diarrhoea, abdominal pain, pharyngitis, cough, dyspnea (with or without rash). While these symptoms overlap those of common infectious illness, the combination of acute onset of both respiratory and gastrointestinal symptoms after starting ABC is more typical of a hypersensitivity reaction. NVP: Systemic symptoms of fever, myalgia, arthralgia, hepatitis, eosinophilia with or without rash.	Discontinue all ARVs until symptoms resolve. The reaction progressively worsens with drug administration and can be fatal. Administer supportive therapy. Do not rechallenge with ABC (or NVP), as anaphylactic reactions and death have been reported. Once symptoms resolve, restart ARVs with change to different NRTI if ABC-associated or to PI- or NRTI-based regimen if NVP-associated.

Adverse Effect	Possible offending drug/s	Clinical signs / symptoms	Management
Severe rash/ Stevens-Johnson syndrome	Non nucleoside reverse transcriptase inhibitors (NNRTIs): nevirapine (NVP), efavirenz (EFV)	Rash usually occurs during the first 2-4 weeks of treatment. The rash is usually erythematous, maculopapular, confluent, most prominent on the body and arms, may be pruritic and can occur with or without fever. Life-threatening Stevens-Johnson Syndrome or toxic epidermal necrolysis (SJS/TEN) has been reported in ~0.3% of infected individuals receiving NVP	Discontinue all ARVs until symptoms resolve. Permanently discontinue NVP for rash with systemic symptoms such as fever, severe rash with mucosal lesions or urticaria, or SJS/TEN; once resolves, switch ART regimen to different ARV class (e.g., 3 NsRTIs or 2 NsRTIs and PI). If rash moderate but not severe and without mucosal or systemic symptoms, change in NNRTI (e.g., NVP to EFV) could be considered after rash resolves.
Severe peripheral neuro-pathy	ddI, d4T, 3TC	Pain, tingling, numbness of hands or feet; distal sensory loss, mild muscle weakness, and areflexia can occur.	Stop suspect NsRTI and switch to different NsRTI that does not have neurotoxicity (e.g., ZDV, ABC). Symptoms usually resolve in 2-3 weeks.

6. CHOICE OF REGIMEN

The choice of regimen depends on a number of factors. These include amongst others, cost of therapy, availability and medium/long term affordability, convenience and likelihood of adherence, regimen potency, tolerability and adverse effect profile, possible drug interactions, and potential for alternate treatment options in the event that the initial drug regimen fails.

Antiretroviral therapy with ***single or dual drug*** *regimen is not recommended due to the rapid emergence of drug resistance.* Monotherapy with zidovudine is recommended for the prevention of mother-to-child transmission of HIV.[43,44] Monotherapy with nevirapine has also shown to reduce mother to child transmission of HIV infection.[45]

Persons doing well on dual NsRTI regimens can be switched to one of the more potent regimens. If this is not feasible or advisable, then treatment should be continued for those persons who are deemed to be benefiting. This, however, is not an endorsement of continued initial use of these regimens and effort should be made to provide standard care regimens to all patients newly initiating therapy.[32]

The use of a protease inhibitor with two NsRTI has shown potent and durable suppression of viral replication.[13,14,46,47] Combination of an NNRTI with 2 NsRTIs also produces viral suppression and immunological improvements which are at least comparable to those seen in combinations that include protease inhibitors.[15,48] Dual protease inhibitor combinations such as ritonavir with saquinavir or other protease inhibitors have also demonstrated potent and durable viral suppression.[49] Ritonavir combined with other protease inhibitors results in increased plasma concentration of these drugs. These combinations have been used with some success although the risks and toxicities are not fully known. Abacavir plus 2 NsRTIs (namely ZDV + 3TC), a triple NsRTI regimen, has been used, but seems to have reduced potency in patients with baseline viral load > 100,000 copies/mL.

Currently, several regimens with acceptable antiviral potency are available. These regimens are composed of three or four drugs. Two NsRTIs generally form the backbone of most combinations.

Possible NsRTI combinations include:

zidovudine + lamivudine

stavudine + lamivudine

zidovudine + didanosine

didanosine + lamivudine

stavudine + didanosine

Zidovudine and stavudine are not used together due to their antagonistic effects.

Zidovudine + lamivudine + abacavir may be combined as 3 NsRTI regimen

The dual combination of stavudine + didanosine should only be used during pregnancy when no other alternatives exist, due to the potential increased risk of lactic acidosis with this combination in pregnant women.

Table 8. *Choice of regimen* [6,7,32,50]

Recommended first line Antiretroviral Regimens in adults and adolescents			
Regimen*	**Recommendation**	**Advantages**	**Disadvantages**
ZDV/3TC plus EFZ or NVP	Recommended	Spares PI Equivalent to PI-based regimens Low pill burden	Limited long-term data NVP may cause severe hepatitis. EFZ is contraindicated in pregnancy
ZDV/3TC/ ABC	Consider for patients with low viral loads (if possible to determine) and adherence concerns	Spares PI and NNRTI Fewer drug interactions Low pill burden	May be less effective in patients with high viral load Limited long-term data Abacavir may cause hypersensitivity reactions
ZDV/3TC plus RTV-enhanced PI (IDV/r, LPV/r, SQV/r) or NFV	Consider	Better pharmacokinetics with RTV-enhanced PI Convenient dosing High potency	Long-term toxicities unknown with RTV-enhanced PI Drug interactions High pill burden with some regimens

*__ZDV/3TC__ is listed as initial recommendation for dual NsRTI component based on efficacy, toxicity, clinical experience and availability of fixed dose formulation. Other dual NsRTI components can be substituted including **d4T/3TC (preferred alternative)**, ZDV/ddI and d4T/ddI depending upon country-specific preferences. ZDV/d4T should never be used together because of proven antagonism. Fixed dose formulations are preferred whenever possible as they promote enhanced drug adherence.

Table 8 is a useful guide to the use of available antiretroviral regimens in individuals with no prior or limited experience of HIV treatment.

Initial regimen of ***2 NsRTI with 1 NNRTI*** is effective, spares PIs, and with low pill burden, is ***often preferred*** over other regimens. A combination of d4T/3TC and NVP is available in a single pill in some countries; it is relatively inexpensive, and may be given twice daily. A regimen containing 3 NsRTIs (abacavir, zidovudine, lamivudine) has twice daily convenient dosing with fewer drug interactions but may be less effective in patients with high viral load. Regimens containing PIs are also effective with long-term data. RTV-enhanced PI regimens have convenient twice daily dosing schedule. However, there is concern about PI-related toxicities and drug interactions.

For Group O HIV-1 subtype or HIV-2 infections, only the triple NsRTI and PI based regimens should be used because of inherent resistance of these viruses to NNRTI compounds.

7. MONITORING THERAPY

Once ART is started, a reasonable schedule for the clinical monitoring includes a first follow-up visit one month after initiation (which may be useful also to evaluate and possibly reinforce adherence to antiretroviral treatment), and a minimum of every three/four months thereafter. Monthly visits, which can be combined with drug dispensing, are encouraged, as they are useful opportunities to reinforce adherence. At each visit, inquiries should be made regarding any new symptoms that may be related to drug side effects, to HIV disease progression or to intercurrent processes. (Please see annex III for proposed patient visit record.)

Adherence

Adherence should be assessed and routinely reinforced.

A high degree of adherence to ARV drugs is necessary for optimal virological suppression. Studies indicate that 90-95% of the doses should be taken for optimal suppression and lesser degrees of adherence are more often associated with virological failure.[51] Maintaining this level of adherence is difficult. Imperfect adherence is common and surveys indicate that one-third of patients missed doses within 3 days of survey.[52]

Factors that are associated with poor adherence include poor patient-clinician relationship, high pill burden, forgetfulness, mental depression, lack

of patient education, inability of patients to identify their medications, drug toxicity and being too ill.[53] Appropriate patient education is essential for a successful ARV programme. Factors associated with good adherence include emotional and practical life support, ability of patients to fit medications into their daily routine, understanding that it is essential to take medications regularly and keep medical appointments.

Important determinants of adherence to antiretroviral therapy in resource limited settings include: [54]

- the quality of initial and continuing counseling resulting in well informed decisions and commitment by the patient to start and maintain antiretroviral therapy.
- the availability of accessible, knowledgeable and committed medical support teams.
- the assurance of affordable and continued supply of antiretroviral medications.
- low pill burden and convenient dosing.

Prior to starting therapy, the patient's **willingness** to take such therapy should be clearly established. A treatment plan should be made which the patient understands and can commit to. The importance of taking medicines on a regular basis and the implications of non-compliance should be explained to the patients. Written instructions should be given to help patients understand the use of prescribed drugs. Possible side effects should be explained in advance. Educating the patient's family and friends may be helpful. A patient suffering from active substance abuse or mental illness may benefit more if these problems are taken care of prior to starting antiretroviral therapy.

A *trusting and caring* relationship between the patient and health care provider is essential. Regular appointments and follow up visits help in the continued care of the patient. Provider attitudes that are supportive and non-judgmental will encourage patients to be honest about their adherence. The healthcare team should have updated knowledge on antiretroviral therapy and adherence, and should undertake training if necessary. New medical problems may influence adherence. Temporary discontinuation of all medicines may be more appropriate than uncertain adherence.

The treatment regimen should be simplified by reducing the number of pills, reducing the frequency of therapy such as twice daily dosing, and minimizing side effects. Simplified regimens improve adherence.

Adherence may be measured by patient self-report, pill count, and the report of the primary care provider.

Questions to assess adherence should include:

- number of doses missed in the last 7 days
- number of doses missed since last visit
- if dose taken at correct time (if no, ask for delay in hours/days)
- if correct dose taken
- specification of reasons for interruption or modification/failure to take prescribed doses.

Monitoring efficacy and toxicity of antiretroviral therapy

The efficacy of antiretroviral drugs is indicated by clinical improvement of the patient, and by rise in CD4 cell counts. It is important also to exclude the occurrence of new HIV-related opportunistic disease since this may mean failure of the current antiretroviral regimen.

Clinical monitoring

Some of the clinical indicators of response to therapy are: [54,55]

- gain in body weight
- decrease in frequency and severity of opportunistic infections

Karnofsky score may be used to assess the clinical status of the patient (please see annex 4).

To promptly diagnose a new or a recurrent HIV-related opportunistic illness as well as drug-related side effects, it is advisable to regularly perform the history taking process regarding the period from the last clinical evaluation.

During history taking, a few questions should be asked regarding:

History taking	Three months	Six months	Nine months	Every three months
HIV related diseases incl. TB	v	v	v	v
Cough > 2 weeks	v	v	v	v
Fever	v	v	v	v
Weight loss	v	v	v	v
Diarrhoea	v	v	v	v
Other symptoms as GI, CNS, neurology, skin rash	v	v	v	v
Other medications taken	v	v	v	v

GI = gastrointestinal tract, CNS = central nervous system

A complete physical examination should be performed during the same visit and should include at least:

Physical examination	Three months	Six months	Nine months	Every three months
BW	v	v	v	v
KS	v	v	v	v
ENT	v	v	v	v
Skin	v	v	v	v
Lymph nodes	v	v	v	v
Respiratory system	v	v	v	v
CVS	v	v	v	v
Abdomen	v	v	v	v
GU	v	v	v	v
Neurology	v	v	v	v

BW = body weight, KS = Karnofsky score, ENT = ear nose throat, CVS= cardiovascular system, GU = Genitourinary tract,

Laboratory investigations

Routine laboratory testing is necessary to monitor drug adverse effects, and appearance of new disease or progression of disease. These may include CBC, serum ALT or AST, serum creatinine, blood glucose, and serum lipids depending on the drug regimen and possible drug adverse effects. At the time of follow up, history and physical examination may indicate other relevant tests.

In ***resource-limited settings*** monitoring of disease progression and response to treatment will be by ***clinical indicators and CD4 cell count.*** It may not be possible to perform viral load due to the cost of the test and lack of laboratory facilities and trained personnel.[56]

Laboratory test	Three months	Six months	Nine months	Every six months
CD4	no	v	no	v
Hb or Hct	v	v	v	v
WBC with diff	v	v	v	v
ALT	v	v	v	v

Hb = haemoglobin, Hct = haematocrit, WBC with diff = white blood cell count with differential

CD4 lymphocyte counts

The clinical manifestations of HIV infection are related to CD4 counts. A low level of CD4 counts, as below 200 cells/mm^3 predicts decreased survival and increased risk of opportunistic infections. CD4 counts are useful to determine when to start therapy and to stop prophylaxis against certain organisms. *In patients with optimal antiretroviral therapy, CD4 counts increase by > 100 cells/mm^3 in the first 6-12 months in ARV naïve, adherent patient with drug susceptible virus.* Higher elevations can be seen and response often continues in subsequent years in the individuals who are maximally virologically suppressed. *Immunologic failure* is indicated by a fall in CD4 counts higher than 30% from the peak value or a return to, or below, the pre-therapy baseline. **A reasonable frequency of CD4 counts measurements in patients on antiretroviral therapy in resource-limited settings is every 6 months**.

Treatment decisions should take into account the clinical condition of the patient, information about adherence and availability of the ARV drugs, results of routine laboratory tests and CD4 counts.

8. CHANGING THERAPY

The reasons for changing an antiretroviral therapy regimen include **drug adverse effects**, **inconvenient regimens** such as dosing/number of pills that may compromise adherence, **treatment failure, occurrence of active tuberculosis and pregnancy**.

The decision to change regimen should be based on clinical history and physical examination; routine and relevant laboratory investigations, CD4 counts and changes in count. An assessment of adherence to medications should be made and remaining treatment options considered. Potential of initial viral resistance, drug interaction and diet will also need to be considered.

8.1 Change Due to Adverse Effects/Intolerance

In a patient who experiences adverse effects or is intolerant to an otherwise successful regimen, substitution of the offending drug is reasonable. An example would be metabolic adverse effects of a PI that can be replaced by an NNRTI. For serious adverse effects, such as abacavir hypersensitivity reactions and nevirapine related hepatic failure, rechallenge should not be attempted as this may lead to toxicity and death (please see chapter on ***serious adverse effects and drug discontinuation*** for details).

8.2 Change due to Treatment Failure

Treatment failure can be defined as clinical failure, immunologic failure and/or virologic failure. **Clinical failure** is defined as clinical disease progression with development of an opportunistic infection or malignancy when the drugs have been given sufficient time to induce a protective degree of immune restoration. This needs to be differentiated from an *immune reconstitution syndrome* which can be seen within the first several weeks after the institution of therapy if a subclinical infection is present at baseline.[57] In *immune reconstitution syndromes*, changing the antiretroviral regimen is not

indicated. **Immunologic failure** can be defined as a fall in CD4 counts higher than 30% from the peak value or a return to, or below, the pre-therapy baseline.[6] There is no accepted definition of immunologic failure that can be used if CD4 counts are not available. **Virologic failure** has no uniformly accepted definition but repeated, continued detectable viremia is indicative of incomplete viral suppression. As measuring viral load in not an option in the majority of resource-constrained settings, it is not recommended for the routine monitoring of treatment in the present guidelines. The reader is referred to other existing guidelines for further reading on the use of viral load to monitor ARV treatment.[6]

Treatment failure may occur due to a number of reasons. These include unsatisfactory patient adherence, viral resistance to one or more drugs, impaired drug absorption, and altered drug pharmacokinetics.

The entire regimen should be changed from a first to a second line combination regimen in the case of treatment failure. ***A single drug should not be added or changed to a failing regimen.*** The new second-line regimen will need to use drugs, which retain activity against the patient's virus strain and ideally include at least three new drugs, in order to increase the likelihood of treatment success.

Table 9 lists the second-line regimens one could consider in adolescents and adults for each of the first-line regimens identified in Table 8.

Nucleoside analog cross-resistance is an increasing concern. When ZDV/3TC is used in the first-line regimen, nucleoside cross-resistance may compromise the potency of d4T/ddI in the second-line regimen, in particular in the presence of long-standing virologic treatment failure. In this regard, ABC/ddI might also be considered as the nucleoside backbone for a second-line regimen if the first line regimen did not include ABC. However, high-level ZDV/3TC resistance also confers diminished susceptibility to ABC.

The near complete cross resistance between EFZ and NVP means that a switch between these two agents in the setting of treatment failure is not advisable. In case of PIs, cross resistance among these agents is also common. A possible exception to this exists when NFV is the first PI employed. Therefore, in the case of treatment failure on a PI-based regimen, it is recommended that the PI be switched to an NNRTI.

Given the diminished potential of almost any second line nucleoside component, a ritonavir (RTV, r) enhanced PI component [indinavir (IDV)/r, lopinavir (LPV)/r, saquinavir (SQV)/r)] is preferred to nelfinavir (NFV) in second line regimens because of its potency. NFV can be considered as an alternative for the PI component if a RTV-enhanced PI is not available or if there is a clinical contraindication to its use.

Table 9. *Recommended second-line regimens in adults and adolescents* [31,32]

First line regimens	Second-line regimens for treatment failure	Alternative second-line regimen for treatment failure
ZDV/3TC plus EFZ or NVP	RTV-enhanced PI [a] + d4T/ddI [b, d]	-RTV-enhanced PI [a] + ABC/ddI [c, d] -NFV + ABC/ddI [c, d] or d4T/ddI [b, d]
ZDV/3TC/ABC	NNRTI [e] + LPV/r +/- d4T/ddI [b, d]	RTV-enhanced PI [a] + d4T/ddI [b, d]
ZDV/3TC/RTV- enhanced PI or NFV	NNRTI [e] + d4T/ddI [b, d]	NNRTI [e] + ABC/ddI [c, d]

[a] RTV-enhanced PI = IDV/r, LPV/r, SQV/r. A RTV-enhanced PI regimen is preferred given the potency of these regimens. NFV can be considered as an alternative for the PI component of second-line therapy if RTV-enhanced PI is not available or if there is a clinical contraindication to its use.

[b] Nucleoside cross-resistance may compromise potency of d4T/ddI at the time of switching for treatment failure as it is assumed that virologic failure will have been prolonged at that point and several nucleoside analog mutations are likely to be present. However, choices are limited in the setting of treatment failure. See also footnote d.

[c] High level ZDV/3TC co-resistance confers diminished susceptibility to ABC.

[d] Tenofovir is a once-daily nucleotide NtRTI with activity against some nucleoside resistant strains. If available, TDF can either be added to d4T/ddI or ABC/ddI or substituted for either d4T or ABC in these combinations. Its current limited availability in resource limited settings is recognized.

[e] NNRTI can be either EFZ or NVP.

9. ANTIRETROVIRAL THERAPY IN SPECIAL SITUATIONS

9.1 Adolescents

Adolescents infected with HIV through sexual route or injecting drug use **during adolescent period**, have a clinical course that is similar to adults. Most of these patients who were HIV infected sexually during the adolescent period are in the **early stage** of HIV infection.[6]

Adolescents infected with HIV as young children either perinatally or through the parenteral route such as blood and blood products may have a different course and may present in **advanced stage** of the disease.[6]

Adolescent < 13 years should receive ART dose based on paediatric guidelines. Adolescents $\geq$ 13 years should receive ART dose based on adult guidelines according to weight.[32]

9.2 Women, with Specific Reference to Pregnancy

ART recommendations for HIV-infected pregnant women are based upon the principle that therapies of known benefit to women should not be withheld during pregnancy unless the risk of adverse effects on the mother, foetus or infant outweighs the expected benefit to the woman.[58] Pregnancy, or the desire to become pregnant, should not preclude the use of optimal antiretroviral therapy. However, considerations related to pregnancy may affect decisions regarding the choice of antiretroviral regimen. Additionally, the potential impact of such therapy on the foetus and infant must also be considered when treating women of childbearing age, unless they use effective contraceptives. For pregnant women who do not yet need ART for their own disease, the use of antiretroviral drugs to reduce the risk of mother-to-child HIV transmission is recommended.[43-45] However, a discussion of ART for this indication falls outside the scope of the present guidelines. The reader is referred to the recent WHO guidelines on prevention of MTCT for further information.

(A) Choice of antiretroviral drugs in non-pregnant women of childbearing age

In non-pregnant women, the recommendations for starting antiretroviral therapy are similar for men and women.[6,50]

The choice of ART in women with the potential to become pregnant must include consideration of the possibility that the ARV drugs may be received during the early first trimester, prior to recognition of pregnancy and during the primary period of foetal organ development. Effective and appropriate contraceptive methods to reduce the likelihood of unintended pregnancy should be available for women receiving ART. NNRTIs (NVP and EFZ) and the PIs (NFV and all low dose RTV-boosted PIs) lower blood concentrations of oral contraceptives and additional or alternative contraception methods need to be used to avoid pregnancy in women receiving these drugs. EFZ may be associated with severe birth defects and should be avoided in women who desire to become pregnant.

(B) Choice of antiretroviral drugs in pregnancy

ARV regimens given for treatment to pregnant women should preferably include drugs shown to be effective in reducing mother-to-child transmission. Drugs shown to be effective in reducing transmission include ZDV, ZDV/3TC, and NVP.[43-45,59-61] The most successful experience in terms of efficacy and maternal and foetal safety is with ZDV; thus, first-line treatment regimens in pregnant women should include ZDV whenever possible. Combination of ZDC/3TC should be the first choice for use in pregnancy. Maternal antiretroviral drugs should be continued during the period of labor.

Pharmacokinetic studies of ZDV, 3TC, d4T, and ddI in pregnant women indicate that the dose used for these drugs in pregnancy should be the same as in non-pregnant individuals.[62-64] ABC has not been formally evaluated in pregnant women. The dual NsRTI combination of d4T/ddI should only be used during pregnancy when no other alternatives exist, due to the potential increased risk of lactic acidosis with this combination in pregnant women.

NVP is the NNRTI of choice for use in pregnancy. Pregnancy should be avoided in women receiving EFZ due to concerns related to teratogenicity and its use should be avoided during the first trimester.

PIs have been associated with the development of glucose intolerance and even diabetes mellitus in non-pregnant individuals. Pregnancy is also a risk factor for hyperglycemia; it is not known if the use of protease inhibitors exacerbates the risk for pregnancy-associated hyperglycemia. Hyperglycemia in pregnancy can lead to an increased risk of macrosomia, foetal distress, pre-

eclampsia and stillbirth. Symptoms of hyperglycemia (e.g., increased urination and thirst, weight loss) should be discussed with pregnant women receiving protease inhibitors and they should be instructed that should such symptoms occur, they should see their health care provider.

NFV, followed by SQV, are the most common protease inhibitors used to treat pregnant HIV-infected women in resource-rich countries.[65] NFV has been well-tolerated by pregnant women; when administered as 1250 mg twice daily it produces adequate drug levels, and is the first choice PI for use during pregnancy.[66] IDV carries the theoretical risk of exacerbating neonatal hyperbilirubinemia if used near to or during labor, and therefore is a less desirable PI choice in pregnancy. LPV/r has not been studied in pregnant women.

(C) Women first diagnosed with HIV infection during pregnancy

Women who are in the first trimester of pregnancy may wish to consider delaying initiation of therapy until after 10-12 weeks gestation due to potential teratogenic effects of ART. Initiation of ART is rarely a medical emergency. However, for women who are severely ill, the benefit of early initiation of therapy may outweigh the theoretical risk to the foetus, particularly if therapy is initiated with drugs in which there is more experience with use in pregnancy (such as ZDV, 3TC, NVP or NFV).

(D) HIV-infected women receiving antiretroviral drugs who become pregnant

For women who become pregnant while receiving ART, the options are to temporarily discontinue therapy during early pregnancy (first trimester), to continue the same therapy, or change to a different drug regimen.

To reduce the potential for emergence of resistance, if it is decided to temporarily discontinue antiretroviral treatment during the first trimester, all drugs should be stopped and restarted simultaneously.

A switch in ART during pregnancy should be considered if the drug being received has teratogenic potential (i.e., EFZ); if there are concerns regarding risk of severe toxicity to the pregnant woman (e.g., d4T/ddI); or

there is significant intolerance of the drug that could be compounded by pregnancy (e.g., gastrointestinal intolerance compounded by morning sickness) and lead to poor drug adherence.

(E) Breastfeeding

Current WHO/UNAIDS/UNICEF guidelines recommend that women with HIV infection be fully informed of both the risks and benefits of breastfeeding and be supported in their decision about feeding practices.

HIV-infected women should preferably avoid breastfeeding to reduce the risk of mother-to-child transmission where safe alternatives are available, affordable and acceptable.[67,68]

However, safe alternatives to breastfeeding may not be available in some resource-limited settings, and in such situations, exclusive breastfeeding for the first 6 months of life is recommended.

Women who require ART and who are breastfeeding should continue their ongoing antiretroviral therapeutic regimen. However, the efficacy of potent ART of the mother to prevent postnatal transmission of HIV through breast milk is unknown.

(F) HIV-infected women who have received short-course antiretroviral prophylaxis to reduce mother-to-child transmission and require treatment postpartum

Short-course ARV drug regimens that do not fully suppress viral replication that are used to prevent MTCT of HIV may be associated with the development of antiretroviral drug resistance. This is most likely to occur with prophylaxis regimens using antiretroviral drugs for which a single point mutation can confer drug resistance, such as NVP or 3TC.

However, based on current information, prior administration of short-course ZDV/3TC or single dose NVP for prevention of mother-to-child transmission should not preclude use of these agents as part of a combination ARV drug regimen initiated for treatment of HIV disease in women.

(G) Issues related to adherence to therapy in pregnancy and postpartum

Adherence to treatment may be more difficult in pregnant and immediately postpartum women than in non-pregnant individuals.[69,70] Potential obstacles to adherence that are unique to pregnancy include morning sickness and gastrointestinal upset, which can be further compounded by ART associated nausea, and fears that antiretroviral drugs might harm the foetus. To reduce the potential for emergence of resistance, if therapy requires temporary discontinuation for any reason during pregnancy, all drugs should be stopped and re-started simultaneously.

The physical changes of the postpartum period coupled with the stresses and demands of caring for a newborn infant may make adherence to treatment especially difficult after birth. Particular attention to provision of additional support for maintaining adherence to therapy during the ante- and post-partum periods is important.

9.3 Tuberculosis

Due to the high prevalence of tuberculosis (TB) among HIV-infected individuals living in the South-East Asia Region, many patients who are candidates for ART will have active TB.[71] 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.[72] The management of HIV and TB co-infection is complicated because some antiretroviral agents produce unacceptable drug interactions with anti-tubercular agents and/or can increase toxicity of TB treatment.[73-75] Tuberculosis treatment following the DOTS strategy should be initiated promptly in diagnosed cases of TB.

The two major issues in the clinical management of patients with HIV and TB are when to start ART and which regimen to use. Initiation of ART for TB patients at very high risk for HIV disease progression and mortality is recommended, i.e., a CD4 count <200 cells/mm^3, or extrapulmonary TB (Table 10). For patients who develop TB with CD4 counts in the 50-200 cells/mm^3 range or, in the absence of CD4 testing, have total lymphocyte counts <1200 cells/mm^3, ART should be started after the first two months of

TB therapy, because the toxicity of TB treatment is greatest during this period (Table 10). In the subset of patients with very low CD4 cell counts (<50 cells/mm^3) or with other severe HIV disease, ART should be started as soon as TB therapy is tolerated.[7]

Table 10. *Antiretroviral therapy for individuals with tuberculosis co-infection*

Situation	Recommendations
Pulmonary TB and CD4 count <50/mm^3 or extrapulmonary TB	Start TB therapy. Start one of these regimens as soon as TB therapy is tolerated: • ZDV/3TC/ABC • ZDV/3TC/EFZ • ZDV/3TC/SQV/r • ZDV/3TC/NVP
Pulmonary TB and CD4 50-200/mm^3 or total lymphocyte count <1200/mm^3	Start TB therapy. Start one of these regimens after 2 months of TB therapy: • ZDV/3TC/ABC • ZDV/3TC/EFZ • ZDV/3TC/SQV/r • ZDV/3TC/NVP
Pulmonary TB and CD4 >200/mm^3 or total lymphocyte count >1200/mm^3	Treat TB. Monitor CD4 counts if available. Start ART according to Table 8.

The first line treatment options include ZDV/3TC or d4T/3TC plus either an NNRTI or ABC. The fixed dose combination of ZDV/3TC/ABC has no drug interactions with anti-tubercular therapy and does not require dose adjustments. However, the hypersensitivity reaction associated with ABC overlaps clinically with the immune reconstitution syndrome (see below) seen with tuberculosis. Therefore, ARV treatment could prematurely and unnecessarily be discontinued in patients with TB who initiate an ARV regimen containing ABC. If an NNRTI based regimen is used, EFZ is the preferred drug as its potential to aggravate the hepatotoxicity of TB treatment appears less than with NVP. The dose of EFZ may need to be increased to 800 mg/day when used in combination with rifampicin. Except for SQV/r, use

of other PIs (NFV, IDV/r, LPV/r) is contraindicated because rifampicin induces hepatic enzymes that reduce exposure to the protease inhibitors to sub-therapeutic levels.

Patients already receiving ART when they develop TB should adjust the regimen to be compatible with TB treatment. Following completion of anti-tubercular therapy, the ART regimen can be continued or changed depending upon the clinical and immunologic status of the patient.

9.4 Other Opportunistic Infections and Hepatitis

Patients who develop opportunistic infections should be treated with ART. Prompt initiation of ART should be considered when opportunistic infections occur for which treatment is not available or in suboptimal, because improvement of the immune system may enhance recovery.[77]

Patients co-infected with hepatitis B or C can be safely treated with several ARV regimens.[78] Because of the possibility of additive hepatotoxicity, regimens with ddI/d4T and/or NVP should be avoided in patients known to have active hepatitis. 3TC and TDF are both active against hepatitis B and may even protect against new infections.[79,80] Patients receiving 3TC or TDF known to have hepatitis B who experience ARV regimen failure may wish to continue these medications when the ARV regimen is switched.

9.5 Immune Reconstitution Syndrome

For many opportunistic infections including TB, there can be a transient worsening of the infection 2-3 weeks after ART initiation; this is referred to as the immune reconstitution syndrome.[81,82] For patients with TB, this syndrome has been reported to occur in as many as 30% of patients in the developed world.[83] The syndrome is characterized by fever, lymphadenopathy, worsening pulmonary lesions (at X-ray examination) and expanding central nervous system (CNS) lesions. These reactions are typically self-limiting, although may require the use of a brief course of corticosteroids to reduce inflammation for severe respiratory or CNS symptoms. Initiation of ART can also unmask previously undiagnosed infections by augmenting the inflammatory response. In general, ART should not be interrupted for immune reconstitution syndromes.

9.6 Prophylaxis for Opportunistic Infections and Tuberculosis

ART is the most effective approach to reducing OI incidence in HIV-infected patients, but should not replace efforts to provide antimicrobial prophylaxis.[10] Co-trimoxazole reduces the risk of bacterial infections, *Pneumocystis carinii* pneumonia and toxoplasmosis and is recommended for all patients who meet indications for ART.[11] In areas with a high prevalence of cryptococcal disease, fluconazole prophylaxis should be considered for patients with less than 100 CD4 cells/mm^3. Based on observations in patients in developed countries, patients responding to ART with a sustained elevation in CD4 cell counts above 200 cells/mm^3 for 3-6 months may discontinue prophylaxis.

Preventive therapy for TB (i.e., treatment of latent TB) reduces the risk for active TB in HIV infected patients, although the durability of this effect may be limited by high rates of re-infection with TB.[84-87] Preventive therapy for TB may not be feasible in many resource-limited settings because of the difficulty in excluding active disease. TB preventive therapy is therefore recommended in areas where diagnostic testing is available to exclude active TB and where PPD skin testing is feasible. In this circumstance, isoniazid therapy (with pyridoxine supplementation) for 9 months in tuberculin skin test reactors is recommended after exclusion of active disease.

10. IMPLEMENTING ARV TREATMENT PROGRAMMES

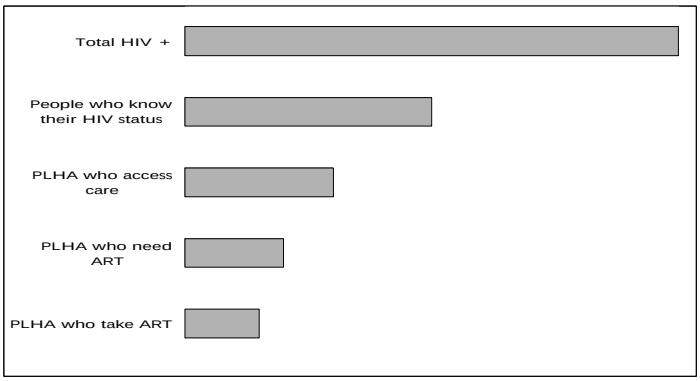
Several components of the implementation process must be considered from the beginning and explored step-wise prior to starting implementation. These include situation assessment, programme planning and implementation steps.

10.1 Situation Assessment

Estimating the burden of any public health problem is an important tool for programme planning. The situation assessment should include a realistic estimate of the burden of HIV infection in the country and in the areas selected for the intervention. An estimate of the total number of people needing ART should be made for programme planning. The need can be estimated from the proportion of people with HIV infection out of the total population of the country or the selected geographical area, the number of people who are estimated to know their HIV status, who access HIV/AIDS

care, who need ART according to the guidelines, and who ultimately will take antiretroviral treatment. An example is given in Figure 1.

Figure 1. ***How to estimate the number of people living with HIV/AIDS (PLHA) to receive ART***



(Note: Affordability includes contribution from government, patient payment, co-payment schemes, health insurance and external resources.)

10.2 Programme Planning

A few steps need to be followed in the planning phase:

- Define clear programme objectives and priorities
- Form technical and community advisory board
- Determine a responsible body and form teams in health care settings
- Plan for sustainability of the programme
- Involvement of PLHA, NGOs, communities and other relevant groups
- Plan ongoing capacity building of health care providers (counsellors, physicians and nurses)
- Define inclusion and exclusion criteria

- Define target groups for ART when funds are limited e.g. patients with active TB, mothers from the PMTCT programmes, people who can not pay
- Select ART regimens and clinical and laboratory tests for treatment monitoring
- Ensure access to ART services
- Ensure adherence to ART
- Ensure referral to other HIV/AIDS care and support services within health facility and community
- Design monitoring, supervision and evaluation tools, plan for data flow and information exchange
- Plan for programme expansion

10.3 Steps for Implementation

Programme level

- Establish/strengthen community and home-based care
- Provide PLHA with education on HIV prevention, care and treatment
- Establish counseling network for ongoing counseling of PLHA and support of counselors
- Establish network for laboratory facilities for developing standard operating procedures (SOP) and quality assurance and quality control (QA/QC) for laboratory tests
- Establish drug procurement, storage and distribution system
- Analysis and feedback of monitoring and evaluation data

Health facility level

Preparation

- Provide capacity building of health care providers (counsellors, physicians, nurses and laboratory technicians)

Components for implementation

- Establish voluntary counseling and testing (VCT) services
- Provide:
  - Pre-treatment screening and enrolment
  - Pre-treatment monitoring for HIV-infected individuals currently not eligible for ART
  - Care package to prevent and treat common OIs
  - ART counseling
  - Treatment monitoring
- Integrate monitoring and evaluation tools
- Establish supervision and support for health care providers

The impact of the ART programme depends on the availability and utilization of VCT, the availability of trained health care workers, laboratory capacity, ART for 1st and 2nd line regimens and funds to sustain the programme.

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Annex 1

INTERIM PROPOSAL FOR A WHO STAGING SYSTEM FOR HIV INFECTION AND DISEASE IN ADULTS AND ADOLESCENTS

Clinical Stage I:

1. Asymptomatic
2. Persistent generalized lymphadenopathy (PGL)

Performance scale 1: Asymptomatic, normal activity

Clinical Stage II:

3. Weight loss, < 10% of body weight
4. Minor mucocutaneous manifestations (seborrheic dermatitis, prurigo, fungal nail infections, recurrent oral ulcerations, angular cheilitis)
5. Herpes Zoster, within the last 5 years
6. Recurrent upper respiratory tract infections (i.e., bacterial sinusitis)

And/or Performance scale 2: symptomatic, normal activity

Clinical Stage III:

7. Weight loss, > 10% of body weight
8. Unexplained chronic diarrhoea, > 1 month
9. Unexplained prolonged fever (intermittent or constant), > 1 month
10. Oral candidiasis (thrush)
11. Oral hairy leukoplakia.
12. Pulmonary tuberculosis, within the past year
13. Severe bacterial infections (i.e., pneumonia, pyomyositis)

and/or performance scale 3: bed-ridden, < 50% of the day during the last month

Clinical Stage IV:

14. HIV wasting syndrome, as defined by CDC [a]
15. *Pneumocystis carinii* pneumonia
16. Toxoplasmosis of the brain
17. Cryptosporidiosis with diarrhoea, > 1 month
18. Cryptococcosis, extrapulmonary
19. *Cytomegalovirus* (CMV) disease of an organ other than liver, spleen or lymph nodes
20. *Herpes simplex virus* (HSV) infection, mucocutaneous > 1 month, or visceral any duration
21. Progressive multifocal leukoencephalopathy (PML)
22. Any disseminated endemic mycosis (i.e. histoplasmosis, coccidioidomycosis)
23. Candidiasis of the oesophagus, trachea, bronchi or lungs
24. Atypical mycobacteriosis, disseminated
25. Non-typhoid Salmonella septicaemia
26. Extrapulmonary tuberculosis
27. Lymphoma
28. Kaposi's sarcoma (KS)
29. HIV encephalopathy, as defined by CDC [b]
    And/or Performance scale 4: bed-ridden, > 50% of the day during the last month

(Note: both definitive and presumptive diagnoses are acceptable.)

[a] HIV wasting syndrome: Weight loss of > 10% of body weight, plus either unexplained chronic diarrhoea (> 1 month), or chronic weakness and unexplained prolonged fever (> 1 month).

[b] HIV encephalopathy: Clinical findings of disabling cognitive and/or motor dysfunction interfering with activities of daily living, progressing over weeks to months, in the absence of a concurrent illness or condition other than HIV infection that could explain the findings.

Annex 2

1993 REVISED CDC CLASSIFICATION SYSTEM FOR HIV INFECTION AND EXPANDED SURVEILLANCE CASE DEFINITION FOR AIDS AMONG ADOLESCENTS AND ADULTS

The revised CDC classification system for HIV-infected adolescents and adults categorizes persons on the basis of clinical conditions associated with HIV infection and CD4+ T lymphocyte counts.

CD 4 lymphocytes	Category A	Category B	Category C
> 500 cells/mm^3	A1	B1	C1
200-499 cells/ mm^3	A2	B2	C2
< 200 cells/mm^3	A3	B3	C3

Category A

- Asymptomatic HIV infection
- Persistent generalized lymphadenopathy
- Acute (primary) HIV infection with accompanying illness or history of acute HIV infection

Category B

Consists of symptomatic conditions in an HIV-infected adolescent or adult that are not included among conditions listed in Category C and that meet at least one of the following criteria: a) conditions are attributed to HIV infection or are indicative of a defect in cell mediated immunity; or b) conditions are considered by physicians to have a clinical course or to require management that is complicated by HIV infection. Examples include, but are not limited to:

- Bacillary angiomatosis
- Candidiasis, oropharyngeal
- Candidiasis, vulvovaginal

- Cervical dysplasia
- Constitutional symptoms such as fever 38.5 °C, or diarrhoea lasting longer than 1 month
- Hairy leukoplakia, oral
- Herpes zoster
- Idiopathic thrombocytopenic purpura
- Listeriosis
- Pelvic inflammatory disease
- Peripheral neuropathy

Category C

This category includes the symptomatic conditions found in patients with AIDS. Examples in this category include:

- Candidiasis of the bronchi, trachea and lungs
- Candidiasis, esophageal
- Cervical cancer, invasive
- Coccidioidomycosis, disseminated or pulmonary
- Cryptococcosis, extrapulmonary
- *Cytomegalovirus* retinitis
- Encephalopathy, HIV-related
- Herpes simplex: chronic ulcer(s) (longer than one month duration); bronchitis, esophagitis or pneumonitis
- Histoplasmosis, disseminated or extrapulmonary
- Isosporiasis, chronic intestinal (greater than 1 month's duration)
- Kaposi's sarcoma
- Lymphoma, Burkitt's (or equivalent term)
- Lymphoma, immunoblastic
- Lymphoma, primary, of brain

- *Mycobacterium avium* complex or *M. kansasii*, disseminated or extrapulmonary
- *Mycobacterium tuberculosis,* any site (pulmonary or extrapulmonary)
- *Mycobacterium*, other species or unidentified species, disseminated or extrapulmonary
- *Pneumocystis carinii* pneumonia
- Pneumonia, recurrent
- Progressive multifocal leukoencephalopathy
- *Salmonella* septicaemia, recurrent
- Toxoplasmosis of brain
- Wasting syndrome due to HIV

Annex 3

PATIENT VISIT RECORD

Patient name or ID

Hospital/clinic number | **Date of visit**

PATIENT HISTORY:

_____ _____

_____

_____

_____

_____

DRUG ALLERGIES _____

ANTIRETROVIRALS: Tick if taken by the patient and circle dose

☐ **ZDV** 300/250 BID ☐ **3TC** 150 BID ☐ **ABACAVIR** 300 BID ☐ **TRIZIVIR** BID

☐ **d4T** 15/20/30/40 BID ☐ **ddI** 250/400 OD ☐ **ddI** 125/200 BID ☐ **COMBIVIR** BID

☐ **NEVIRAPINE** 200 BID ☐ **EFAVIRENZ** 600 OD

☐ **Combination d4T** 40/30/**3TC/NVP** BID

☐ **IDV** 800 BID / **RTV** 100 BID ☐ **SQV** 1000 **/ RTV** 100 BID ☐ **NFV** 1250 mg BID

☐ **TENOFOVIR** 300 QD ☐ **OTHER** (specify) _____

Is there any change since last visit? ☐ no ☐ yes if **yes**, specify

_____

_____

ADHERENCE TO ANTIRETROVIRAL THERAPY:

N° of doses missed in last 7 days: ..... N° doses missed since last visit: .....

Dose taken at **correct time**: ☐ yes ☐ no **Correct dose** taken: ☐ yes ☐ no **Dose delay** > 1 hour: ☐ yes ☐ no

Specify reason for interruption or modification / failure to take prescribed doses:

OTHER MEDICATION: new and ongoing (If new, indicate Start Date)

MEDICATION	START DATE (tick if ongoing from last visit)	COMMENTS
cotrimoxazole (960 mg OD)	___/___/___ ☐	_____
INH (300 mg OD)	___/___/___ ☐	_____
fluconazole (200 mg 2/week)	___/___/___ ☐	_____
azithromycin (1250 mg/week)	___/___/___ ☐	_____
_____	___/___/___ ☐	_____
_____	___/___/___ ☐	_____
_____	___/___/___ ☐	_____
_____	___/___/___ ☐	_____
_____	___/___/___ ☐	_____

Body Weight _____**kg** **Pulse** _____**bpm** **BP** _____ **Temp** _____**°C Resp Rate**_____

PHYSICAL EXAMINATION: (tick if normal, describe if abnormal)

☐ General	.....	☐ Skin	.....
☐ ENT	.....	☐ Lymph nodes	.....
☐ Heart	.....	☐ Resp	.....
☐ Abdomen	.....	☐ GU	.....
☐ Musculoskeletal	.....	☐ Extremity	.....
☐ Neuro	.....	☐ Other (describe)	.....

HIV-RELATED ILLNESSES: new and ongoing (If new, indicate Start Date)

Are there any new HIV-related illnesses at this visit? ☐ no ☐ yes if **yes**, specify

	START DATE		COMMENTS
☐ oral candidiasis	___/___/___	☐	_____
☐ oral hairy leukoplakia	___/___/___	☐	_____
☐ pruritic papular eruption	___/___/___	☐	_____
☐ lymphadenopathy (> 1 cm on both sides)	___/___/___	☐	_____
☐ other HIV related illnesses:			
_____	___/___/___	☐	_____
_____	___/___/___	☐	_____

BASIC LABORATORY RESULTS

Haemoglobin _|_|.|_| g/dl WBC _|_|.|_|_| 10^3cells/µl Platelets _|_|_|_| 10^9/l

Total lymphocyte count _|_|.|_|_| 10^3cells/µl

Glucose _|_|_|_| mg/dl Creatinine _|_|.|_|_| mg/dl

ALT/ SGPT _|_|_|_| U/l

CD4+ cells _|_|_|_| /µl HIV-1 RNA _|_|_|_|_|_|_| copies/ml

Other lab results (e.g. CXR, AFB, culture, serology)

_____ _____

_____

_____

WHO Stage: ☐ I ☐ II ☐ III ☐ IV

CDC classification: ☐ A ☐ B ☐ C Any disease progression ☐ no ☐ yes

NOTES/PLAN: _____

_____

_____

_____

Follow-up Date:_____

This has to be considered an example taken from the Region; it has already been used in the Region, however it can be adapted to each local situation and monitoring and reporting system in use.

Annex 4
KARNOFSKY SCORE

Physical Ability	Score
Normal	100
Independent with minimal symptoms	90
Independent with more efforts and symptomatic	80
Can do only activity of daily living	70
Partially independent	60
Partially dependent and require more medical treatment	50
Dependent with specific care	40
Totally dependent, require hospitalization and not impending to die	30
Moribund, needs hospitalization with full medical treatment	20
Comatose	10
Death	0

Annex 5

PLASMA HIV RNA ASSAY

Plasma HIV RNA assay (viral load) is a useful test to monitor antiretroviral therapy.

The viral load can be determined by the following methods:

(1) Amplicor HIV-1 Monitor test and Amplicor HIV-1 UltraSensitive Monitor test (Roche)

(2) Quantiplex HIV-1 RNA 3.0 (bDNA, Chiron)

(3) NucliSens HIV-1 QT (NASBA, bioMerieux/Organon)

Roche Amplicor HIV-1 Monitor test and Amplicor HIV-1 UltraSensitive Monitor test are polymerase chain reaction (PCR) based assay for quantitative measurement of HIV RNA in plasma. The Amplicor HIV-1 Monitor test is reproducible at 400 HIV RNA copies per ml of plasma and has an upper limit of 750,000 copies. The UltraSensitive Monitor test has a range of 50 copies/ml up to 75,000 copies.

The branched DNA (bDNA) Quantiplex HIV-1 RNA 3.0 produced by Chiron Diagnostics is based on signal amplification and utilizes DNA synthetic probes to measure viral load. The Quantiplex HIV-1 RNA 3.0 assay has a detection range from 50 copies/ml to 500,000 copies/ml.

NucliSens HIV-1 QT is based on nucleic acid sequence based amplification (NASBA). The assay amplifies a target area on HIV, or a sequence. The lower limit of detection is 40 copies/ml and the upper limit is 5,000,000 copies/ml.

The viral load usually decreases rapidly after starting therapy and 1.5 to 2.0 log reduction should occur by 4 weeks. Achieving an early response at 8 week is predictive of subsequent viral suppression. Viral load should continue to decline over the following weeks and in most patients becomes undetectable by 16-20 weeks. If HIV RNA remains detectable in plasma after 16-20 weeks of therapy, the plasma HIV RNA test should be repeated to confirm the result. Failure to reach undetectable level should cause consideration of poor adherence, inadequate drug absorption or drug resistance.

For further details the reader is referred to published guidelines.[6]

Annex 6

USEFUL INTERNET LINKS

- http://www.who.int/HIV-AIDS/first.html
- http://www.who.int/medicines/organization/qsm/activities/pilotproc/pilotproc.shtml
- http://www.who.int/medicines/organization/par/edl/expertcomm.shtml
- http://www.medscape.com/Home/Topics/AIDS/AIDS.html
- http://www.amfar.org
- http://www.hivandhepatitis.com
- http://www.bnf.org/AboutBNFFrameHowtoUse.htm
- http://www.cdc.gov/hiv/treatment.htm
- http://www.ama-assn.org/special/hiv/hivhome.htm
- http://www.fda.gov/oashi/aids/hiv.html
- http://www.hivatis.org
- http://www.hopkins-aids.edu/
- http://www.aidsmeds.com/
- http://www.aidsmap.com
- http://aids.org
- http://www.thebody.com/
- http://www.hivnat.org/
- http://hivinsite.ucsf.edu/InSite
- http://www.paho.org/English/HCP/HCA/antiretrovirals_HP.htm
- Web sites of drug companies manufacturing antiretroviral drugs