MINISTRY OF HEALTH MALAYSIA

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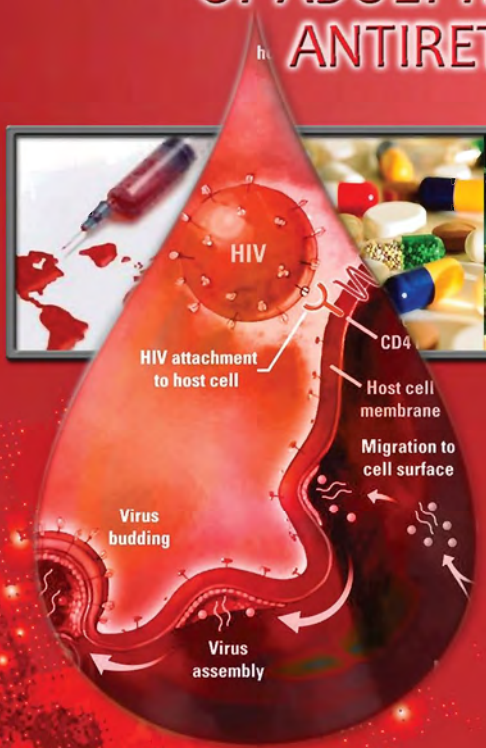
GUIDELINES FOR THE MANAGEMENT OF ADULT HIV INFECTION WITH ANTIRETROVIRAL THERAPY



Medical Development Division
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GUIDELINES FOR THE MANAGEMENT OF ADULT HIV INFECTION WITH ANTIRETROVIRAL THERAPY

This guideline was developed by the Medical Services Unit, Medical Development Division, Ministry of Health Malaysia and the Drafting Committee of Guidelines for the Management of Adult HIV Infection with Antiretroviral Therapy.

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Their commitment and support made the development of this document possible.

Message from
DIRECTOR GENERAL OF HEALTH

It has been 30 years since HIV was first recognized as a public health menace. It remains till today a lethal disease that brings misery and suffering both to the infected person as well as to his community and country. Malaysia has not been spared of this phenomenon. Thankfully, the field of HIV medicine has seen exciting developments over the last few years.

The emergence of highly active antiretroviral therapy in the mid 90's has meant a profound improvement in the prognosis of HIV sufferers worldwide, changing HIV from a lethal infection to a chronic, controllable condition. Since then, the challenge among HIV care providers has been to engage HIV infected individuals at an earlier stage of their disease so as to initiate earlier treatment before the disease reaches a life threatening stage and to utilize medications that have minimal long term adverse effects. Ensuring patients remain under active follow-up and treatment has also been an essential tool in maintaining optimal health and preventing emergence of HIV resistance.

With the advent of a greater understanding of this disease and newer treatment modalities, the World Health Organisation (WHO) in 2010 launched a revision to the recommendations of antiretroviral therapy for HIV infected adults and adolescents. Among the major recommendations are changes in the CD4 levels for initiating antiretroviral therapy and the use of safer antiretroviral agents.

On the local front, it is heartening to see many newer drugs being made available and the reduction in prices of older medications. Indeed, since 2006, Malaysians have been able to access highly active antiretroviral therapy for free. With access to CD4 counts and viral loads being made universal in our country, it is our hope that people living with HIV/AIDS in our country will receive a standard of care that is equivalent to the developed world.

With this many changes, it is timely that a 3rd edition of the Guidelines for the Management of Adult HIV Infection with Antiretroviral Therapy replace the previous edition which saw print in 2001, and which was subsequently revised in 2004.

I congratulate members of the committee, who comprise of Infectious Disease Physicians from both the Ministry of Health as well as University Hospitals under the auspices of with the Malaysian Society for HIV Medicine, in producing this guideline. I believe this document will be an essential guide for clinicians in making important therapeutic decisions in managing individual patients.

DATO' SRI DR. HASAN BIN ABDUL RAHMAN

Message from
DEPUTY DIRECTOR GENERAL OF HEALTH (Medical)

The fi eld of HIV has changed in leaps and bounds in recent years. While the prognosis for someone infected with HIV now is very much improved compared with the past, HIV remains a tricky and complicated disease to manage.

The epidemiology of HIV in our population continues to evolve and with this, we are seeing different of society being victims to this disease. With this ever changing epidemiology, there is also a need to address patients with comorbidities such as Tuberculosis, Hepatitis B, Hepatitis C and patients with active substance abuse.

With regards to antiretroviral drugs in our country, there are now newer medications, combination tablets, once-a-day drugs and drugs with minimal long term adverse events.

With these changes in mind, it is opportune for the Ministry of Health to produce a 3rd edition of the Guidelines for the Management of Adult HIV Infection with Antiretroviral Therapy. A separate guideline exists for the prevention of maternal to child transmission of HIV and is complementary to this guideline. It must be remembered though that guidelines do not replace the need for sound individual judgement on the part of the managing physician. While the expert panel has taken pains to be specifi c where they could, individualization of care must always be practiced.

I would like to thank the members of the panel in their untiring efforts to produce this guideline and to the secretariat for the support and services provided.

DATUK DR. NOOR HISHAM ABDULLAH

CONTENTS

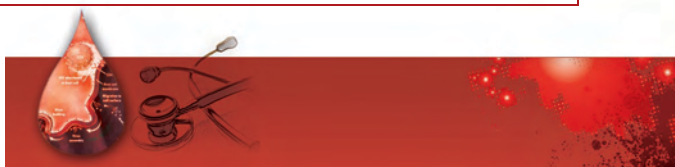
Principles of Antiretroviral therapy

Infection with Human Immunodefi ciency Virus (HIV) leads to progressive immune destruction as a result of persistent viral replication. Antiretroviral therapy has been shown to decrease viral replication, increase CD4+ T-cell count, decrease the frequency of opportunistic infections, improve quality of life and prolong life expectancy of HIV infected patients.

Although the concept of actual eradication remains speculative at this time, signifi cant progress in antiretroviral therapy has brought forth the concept of HIV infection as a chronic, manageable condition.

In Malaysia, there are 6 groups of antiretroviral agents that are available:

1.	**Nucleoside Reverse Transcriptase Inhibitors(NRTI)/Nucleotide Reverse Transcriptase Inhibitors (ntRTI)**
	a. Zidovudine (AZT) b. Didanosine buffered(ddI) or enteric coated(ddI EC) c. Stavudine (d4T) d. Lamivudine (3TC) e. Abacavir (ABC) f. Tenofovir (TDF) g. Emtricitabine (FTC) (available as combination with tenofovir)
2.	**Non Nucleoside Reverse Transcriptase Inhibitor (NNRTI)**
	a. Nevirapine (NVP) b. Efavirenz (EFV) c. Etravirine (Intelence)
3.	**Protease Inhibitors (PI)**
	a. Indinavir (IDV) b. Lopinavir/ritonavir (Kaletra) c. Saquinavir d. Atazanavir (ATV) e. Darunavir (Prezista) f. Ritonavir g. Nelfi navir (Viracept)
4.	**Integrase Inhibitors**
	a. Raltegravir (Isentress)
5.	**CCR5 Antagonists**
	a. Maraviroc (Celsentri)
6.	**Fusion Inhibitor**
	a. Enfuritide (Fuzeon)



With the rapid advancement of HIV medicine, the principles of antiretroviral use have evolved. Therefore, there is a need to redefi ne these principles.

1. Highly active antiretroviral therapy (ART) using 3 or more active anti HIV drugs from at least 2 different class with the aim of achieving durable viral suppression to undetectable levels, is the therapeutic goal under most clinical circumstances.

    a. The goal of potent and durable viral suppression is very important regardless if it is the fi rst or subsequent regimen. A failing regimen generally requires a change of two, or preferably three new drugs with no cross resistance with agents in previous regimens. Adding or substituting only one new medication is not recommended.

    b. In certain circumstances it is diffi cult to formulate a regimen to achieve full suppression especially in patients with multi-resistant virus, drug intolerance and unmanageable allergies. In these instances, limited viral suppression may still confer clinical benefi t to the patient.

2. The initiation of antiretroviral therapy must be a carefully planned decision following thorough evaluation and informed discussion between the healthcare provider and the patient.

    a. The patient's willingness to initiate and adhere to treatment is of the utmost importance. This should be done with the patient's full comprehension of the rationale of treatment

    b. The patient should understand
        - the need for strict adherence and regular medical follow up,
        - the adverse effects and immune reconstitution associated with treatment their implications and management
        - the antiretroviral options available to the patient.

3. The regime must be based on factors related to the patient and the virus with long term disease control as the major goal. Regimen should be individualised, after assessment of the following:

    a. Drug-drug interactions, dosing frequency and pill burden

    b. patient factors that may hinder adherence, e.g. irregular working hours, depression, gastrointestinal disturbance, etc,

    c. viral factors that will suggest resistance, e.g. acquisition of HIV from a partner who is on treatment,

    d. underlying risk factors or disease that will predispose to adverse effects of antiretroviral agents e.g. cardiovascular risk factors, metabolic syndrome, diarrhoea, etc.

4. ART should be prescribed only by doctors with training in the management of HIV disease

   a. The complexity of antiretroviral treatment, the lifelong commitment of patients to such therapy, and the risk of drug resistance mandates prescription only by trained doctors.

   b. antiretrovirals to be used in a setting where there is adequate laboratory support especially the measurements of viral load and CD4 count .

There are many international guidelines available for antiretroviral therapy. However, this local guideline will provide rational use of antiretroviral agents based on local availability and cost considerations.

Assessment and Management of Adults with HIV Infection

Initial assessment and management of newly diagnosed patients

All patients on entering initial care should have a detailed medical history, physical examination and laboratory evaluation performed. The aim is to confi rm the presence of HIV infection, to stage the HIV disease according to WHO staging, to determine the existence of co infections / opportunistic infections (OIs) and to assess overall health.[1]

Table 1 : Initial assessment and management of newly diagnosed patients

Key headings	
Clinical assessment	- Complete history and examination (including weight and blood pressure), including assessment of features of seroconversion or symptomatic late stage disease. - Assessment of duration of HIV infection if possible.
Assessment of Social context	- Risk factors for transmission, including sexual history, injecting drug use, prior surgery or blood transfusion, occupation - Level of understanding of HIV infection and its consequences - Community situation – occupation, family/social networks, cultural/religious context
Assessment of psychology impact	- Factors leading to increased risk of suicide, depression or adjustment disorder following diagnosis ; - Past psychiatric morbidity, injecting (and other) drug use, alcohol dependence, prior maladaptive illness - Behaviour, cultural/religious factors - Disclosure of diagnosis to others - Screening for depression and other psychiatric morbidity
Investigation for co-morbidities and co-infections	- Screening for sexually transmitted infections (gonorrhoea, chlamydia, syphilis. - Evaluation of viral hepatitis co-infection - Cervical cytology (Pap smear) in women - Chest X-ray/Mantoux test if clinically indicated - Evaluation and recording of cardiovascular risk factors
Health maintenance	- Nutritional assessment and intervention - Vaccination – consider HAV, HBV, pneumococcal vaccination (if CD4 > 200), seasonal infl uenza vaccination - Regular cervical cytology (12 monthly) - Co-trimoxazole prophylaxis

Education and support	- HIV transmission, natural history, treatment - Counselling, including partners where this is requested - Reproductive/contraceptive advice and counselling for women and discordant couples - Referral to other disciplines as required e.g. dietician, social worker, substance abuse agencies - Referral to peer support agencies
Risk assessment and prevention	- Education, counselling and interventions regarding safer sexual practices and injecting techniques - Detailed risk assessment, at least annually (including sexual practices and alcohol and drug use) - Regular STI screening as indicated by risk assessment
Public health measure	- Notification of new HIV diagnosis - Partner notification/contact tracing – can be done by patient or clinician or by local public health offi cers - Notification of other notifiable infections e.g. syphilis, HBV, HCV - Advice to patient regarding legal obligations around disclosure of HIV status to sexual partners. - Occupational advice e.g. HCW and exposure-prone procedures, sex worker.

Adopted from: HIV Management in Australasia a guide to clinical care 2009

Laboratory Monitoring While on Antiretroviral Therapy (also see table 2)

CD4 Count:

Successful therapy is defined as an increment in CD4 cell count that averages 100–150 cells/mm^3 per year with an accelerated response in the fi rst 3 months. This is largely due to redistribution .CD4 will increase approximately 100 cells/mm per year for the subsequent few years until a threshold is reached.[1]

CD4 counts should be monitored every 3–4 months to:

a. Assess immunologic response to antiretroviral therapy
b. Assess the need for initiation or discontinuation of prophylaxis for opportunistic infections

Once CD4 cell counts are consistently above 350/microL, less frequent monitoring of CD4 cell count (i.e. every 6 months) is reasonable if the viral load remains suppressed.[2]

HIV Viral Load

Plasma HIV-1 RNA should be measured at the time of ART initiation. However it is not recommended as a guide to initiate ART. HIV-1 RNA is useful for monitoring response to ART.

Plasma HIV-1 RNA should be measured:

a. just before initiation of ART
b. before changing treatment regimes due to failure of therapy
c. every 4-6 months during stable ART

Effective therapy should generally result in at least a 10-fold (1.0 $\log_{10}$) decrease in HIV-1 RNA copies/ml in the first month and suppression to less than 50 copies/ml by 16-24 weeks.[3] A confirmed rebound in plasma HIV-1 RNA level after achieving an undetectable level should prompt a careful evaluation of the patient's adherence to the treatment regimen.

Monitoring other parameters (Refer Table 2)

The frequency of monitoring depends on the response to ART and the choice of drugs. At the minimum, however, monitoring should take place at 4, 8, 12 and 24 weeks after ART initiation and should subsequently be performed every 4-6 months once the patient has been stabilized on therapy.

At each visit, monitoring need to be complimented by assessment of treatment side effects and adherence.

Table 2 : Laboratory assessment and monitoring

***This table is meant to serve as a general guide and should not replace clinical judgement for individual patients. Laboratory monitoring is warranted outside this schedule if there is presence of any signs and symptoms suggestive of medication-related toxicities. Detection of abnormalities on laboratory testing should not necessarily lead to automatic discontinuation or modification of the ART regimen; rather, the results should be interpreted in the context of the patient's clinical signs and symptoms or be repeated if clinically inconsistent. Consultation with an Infectious Disease physician is recommended.*

Laboratory parameters	Entry into care	Pre ART	Post ART : frequency of monitoring	Drugs of special concern
CD4			Every 4 months after starting ART When stable on treatment every 6 months	
HIV viral load	X	(pre treatment baseline VL)	Repeat every 4 months after initiation (should achieve VL<50 by 16-24 weeks) When stable on treatment to consider VL every 6 months	
Full blood count			Before initiation and every 4-6 month after that.	AZT is associated with bone marrow suppression; onset is within weeks to months. If on AZT - before initiation and at week-4, 8 and 12 on therapy or in response to symptoms.
Liver function test, including transaminases			Before initiation and every 4-6 months after that.	NRTI and NNRTI drugs can cause hepatotoxicity. If on NVP, ALT need to be monitored more frequently; at baseline, 2, 4, 12 weeks and then every 3- 6 months Obtain ALT in patients with new onset of rash.
Serum lactate	X	X	When hyperlactaemia or lactic acidosis is clinically suspected. Routine monitoring of lactate level is generally not recommended.	Lactic acidosis is a rare but severe complication of NRTI therapy caused by mitochondrial dysfunction. The risk is highest in regimens containing d4T.
Fasting lipid profi le and fasting glucose			Every 6-12 months.	EFV, NRTIs, PIs (with the exception of unboosted atazanavir), can cause insulin resistance and dyslipidaemia.

Renal function test			Every 6 months If patient is on TDF, 8 weeks post therapy and then every 4 months; include serum phosphate	Renal tubular dysfunction is associated with TDF. Routine monitoring of calculated creatinine clearance and serum phosphate should be performed in patients at risk for renal impairment. Nephrolithiasis is commonly seen with IDV.
Urinalysis	X	(if starting on TDF)	Repeat every 12 months if patient on TDF.	
Urine pregnancy test	X	(if starting on EFV)	When clinically indicated	EFV is associated with teratogenicity

Co-trimoxazole prophylaxis

Co-trimoxazole is recommended for *Pneumocystis jiroveci pneumonia* (PCP) prophylaxis to all susceptible individuals as it has been shown to decrease the risk of PCP by nine fold in this population.

Table 3 : PCP prophylaxis

When to commence primary co-trimoxazole prophylaxis*	HIV-infected adults and adolescents, including pregnant women with • CD4+ T lymphocyte count of <200/µL or (CD4+ T lymphocyte percentage of <14% • history of oropharyngeal candidiasis • unexplained fever of more than two weeks duration
Secondary co-trimoxazole prophylaxis	Secondary prophylaxis for the prevention of relapse is recommended for all patients who have completed successful treatment for *Pneumocystis jiroveci* pneumonia (PCP).
Timing the initiation of co-trimoxazole in relation to initiating ART	Start co-trimoxazole prophylaxis first. Start ART two weeks later if the individual tolerates cotrimoxazole and has no symptoms suggestive of allergy (rash, hepatotoxicity).
Dosages of co-trimoxazole in adults and adolescents	One double-strength tablet or two single-strength tablets once daily. Total daily dose is 960 mg (800 mg sulfamethoxazole [SMZ] + 160 mg trimethoprim [TMP]).
Co-trimoxazole in pregnant/lactating women	Women who fulfil the criteria for co-trimoxazole prophylaxis should continue on it throughout their pregnancy. If a woman requires co-trimoxazole prophylaxis during pregnancy, it should be started regardless of the stage of pregnancy.
Patients allergic to sulfa based medications	Dapsone 100 mg per day can be given. Co-trimoxazole desensitization may be attempted but not in patients with a previous history of severe reaction to co-trimoxazole or other sulfa-containing drugs.
Monitoring	No specific laboratory monitoring is required for patients receiving co-trimoxazole.
Universal option	Co-trimoxazole prophylaxis may be considered for all patients with active TB and who are HIV positive from certain high-risk populations such as IDUs and sex workers who typically present late with advanced disease and are less likely to have access to facilities with CD4 counts.

** Guidelines for the Prevention of Opportunistic Infections Among HIV-Infected Persons – 2002 Recommendations of the U.S. Public Health Service and the Infectious Diseases Society of America*
§ This will help in differentiating between the similar side-effects caused by Co-trimoxazole and ART (especially if starting an NVP-containing regimen).

Co-trimoxazole desensitization

Co-trimoxazole desensitization has been shown to be successful and safe in approximately 70% of patients with previous **mild-to-moderate** hypersensitivity. Desensitization should not be attempted in individuals with a previous history of severe reaction to Co-trimoxazole or other sulfonamides. If a reaction occurs, the desensitization regimen should be stopped. Once the patient recovers fully, Dapsone 100 mg per day may be tried.

Table 4 : Protocol for co-trimoxazole desensitisation

Step	Dose
Day 1	80 mg SMX + 16 mg TMP (2 ml oral suspension)
Day 2	160 mg SMX + 32 mg TMP (4 ml oral suspension)
Day 3	240 mg SMX + 48 mg TMP (6 ml oral suspension)
Day 4	320 mg SMX + 64 mg TMP (8 ml oral suspension)
Day 5	One single-strength SMX–TMP tablet (400 mg SMX + 80 mg TMP)
Day 6	Two single-strength SMX–TMP tablets or one double-strength tablet (800 mg SMX + 160 mg TMP)

Source: Guidelines on co-trimoxazole prophylaxis for HIV-related infections among children, adolescents and adults in resource-limited settings: recommendations for a public health approach. Geneva, World Health Organization, 2006.

Note: *Co-trimoxazole oral suspension contains 200 mg SMX + 40 mg TMP per 5 ml.*

Initiating antiretroviral therapy in treatment naïve patients

When to start ART

Primary HIV infection

There is no adequate data on the clinical benefi t of antiretroviral therapy in Primary HIV Infection (PHI)

Symptomatic HIV infection

ART is indicated in all symptomatic HIV patients regardless of their CD4 count. Individual who has AIDS-defi ning illness or signifi cant wasting, prolonged fever or candidiasis is heralded to develop deterioration in immunology response. ART therapy is important to restore the immune function.

Asymptomatic HIV infection

The decision to initiate ART in asymptomatic patients is largely depended on their CD4 count. There is clear indication to start ART in patient whose CD4 count is less than 200 cells/mL .

ART is also recommended in patients with CD4 200-350 cells/mL. Data from the ART Cohort Collaboration showed that, at 3 to 5 years after starting therapy, the risk for AIDS/death was signifi cantly less in those who started therapy with a CD4 cell count between 200 and 350 compared with those who initiated ART at a CD4 <200[7].

Even though some studies have demonstrated potential benefit in initiating ART at CD4> 350cells/uL[8], the risk of progression to AIDS and death is small at this level of CD4 count[8]. Hence, decision to commence ART at a very early stage need to be balanced with plausible problems of pill burden, drug toxicity, emergence of resistance and drug durability. Therefore, in general ART is not recommended in patient with CD4 > 350cells/uL.

Table 5 : Recommendations for initiation ART in treatment naive patients

	CD4 Count	Recommendation
Symptomatic (AIDS defi ning illness according to WHO classifi cation)	Any value	To treat
Asymptomatic	<200 cells/mL	To treat
Asymptomatic	200-350 cells/mL	Treatment is recommended
Asymptomatic	>350 cells/mL	Not to treat *

** Consider ART in patients with CD4>350cells/uL but CD4 %< 14%.*

Discordant CD4 cells count and fraction of CD4 (%)

CD4 percentage at initiation of the first ART regimen predicts disease progression and mortality independent of absolute CD4 count[9]. Hence, ART can be considered in patients whose CD4>350cells/uL but CD4 % <14%[10].

When to start ART after an acute opportunistic infections (OIs)

Starting ART in the event of acute OIs remains a great challenge. Delaying ART till completion of OI therapy would increase the risk of progression to AIDS and death. Compounding this are the problems of drug–drug interactions, additive adverse effects, high pill burden, patient adherence and paradoxical reactions.

This guideline recommends clinical assessment at the end of 2 weeks of OI therapy . If patient is stable and has improved with the OI treatment, ART can be considered at this time[11].

However, in patients with severe or extensive OIs, ART therapy may be delayed till 4 to 8 weeks later. The delay is to allow adequate time for the anti-microbials to remove the antigenic load. This would reduce the incidence of IRIS.

Once patients have been started on ART, careful surveillance must be practiced to look for reactivation of OIs (IRIS) or emergence of new OIs.

However, in patients with OIs for which no effective treatment is available (cryptosporidiosis, microsporidiosis, progressive multifocal leukoencephalopathy, and Kaposi's sarcoma), ART itself can result in improvement and hence should be initiated as soon as possible.

When to start ART in patients with co-morbidities

1) Chronic hepatitis B or C – (Refer HIV and co-infections)
2) Tuberculosis – (Refer HIV and co-infections)
3) HIV – associated nephropathy (HIVAN)

   HIVAN is a condition characterized by heavy proteinuria and a rapid decline in renal function. It is caused by HIV infection and expression of viral genes in renal epithelial cells .Ongoing viral replication results in renal injury irrespective of CD4 count. Antiretroviral therapy could slow its progression and prolong survival[12]. Therefore, ART should be initiated for patients with HIVAN regardless of their CD4 cell count.

What to start:

Factors to Consider When Selecting an Initial Regimen

Regimen selection should be individualized, and should consider a number of factors including:

1. Co morbidity (e.g., cardiovascular disease, liver disease, viral hepatitis status, psychiatric disease, renal diseases, or tuberculosis);
2. Patient adherence;
3. Convenience (e.g., pill burden, dosing frequency, food and fl uid considerations);
4. Potential adverse drug effects;
5. Potential drug interactions with other medications;
6. Pregnancy potential;
7. Gender and pre treatment CD4 T-cell count when considering Nevirapine

Box 1: Principles of selecting ART for fi rst line regime

Principles for selecting the first-line regimen
1. Choose Lamivudine(3TC) in all regimens
2. Choose one NRTI to combine with 3TC (AZT or TDF or d4T)
3. Choose one NNRTI (NVP or EFV)

Choice of nucleoside reverse transcriptase inhibitors (NRTI)

While AZT, TDF and d4T are comparable in terms of effi cacy, AZT and TDF are currently preferred[3]. This is because d4T has consistently been associated with lactic acidosis, lipoatrophy and peripheral neuropathy. However d4T may still be used as a substitute for AZT if intolerance occurs and if TDF is not available. Early recognition of d4T side-effects and switching to an alternative NRTI may reduce the incidence of these side effects. In addition consider switching d4T to AZT after the fi rst 6 months to avoid the long term adverse events of d4T.

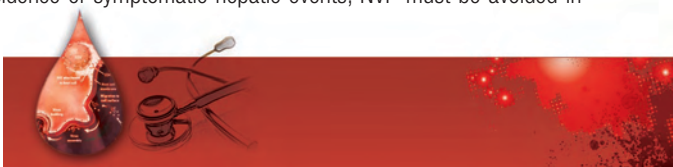
Choice of Non-nucleoside reverse transcriptase inhibitors (NNRTI)

Nevirapine:

Lead-in NVP dose for the first 2 weeks: Start NVP 200 mg once daily for the first 14 days. If there is no rash and there are no signs of hepatic toxicity, increase the dose to 200 mg twice daily. Starting treatment with a reduced dose is necessary because during the fi rst two weeks of treatment NVP induces its own metabolism. The lead-in dose also decreases the risk of rash and early NVP-induced hepatitis. If NVP is restarted after more than 14 days of treatment interruption (due to adverse effects, e.g. elevated liver enzymes), the lead-in dosing is recommended.

The initiation of NVP at the same time as other new drugs that can cause rash (e.g. co-trimoxazole) should be avoided if possible.

In view of the signifi cant increase in incidence of symptomatic hepatic events, NVP must be avoided in



women with baseline CD4 count > 250 and for men with baseline CD4 count > 400.

Refer **Table 2** : Laboratory assessment and monitoring while on nevirapine

Refer **Annex 6** for management of Nevirapine associated skin rash and hepatotoxicity

Efavirenz:

Efavirenz is preferred over nevirapine:

- in patients with TB/HIV co infection receiving rifampicin
- In patients with clinical and/or laboratory evidence of signifi cant (grade 3 or 4) hepatic dysfunction.

Stopping / Interrupting NNRTI

NNRTIs have low genetic barrier to resistance with long half lives. Long half-lives may prevent resistance with delayed or missed doses, but there is a high risk of resistance with treatment interruptions. Because of the long half-life of NNRTIs (40-160 hrs) compared with NRTIs (0.5-17hrs) abrupt discontinuation of a regimen containing EFV or NVP can lead to periods of NNRTI "monotherapy'" with risk of NNRTI resistance.

Box 2: Stopping either nevirapine (NVP) or efavirenz (EFV)

- Stop NVP or EFV.
- Continue NRTI backbone (2 drugs only) for 7 days then stop all drugs

Also refer **Annex 2 : ARV combinations that are not recommended**

Guidelines on counselling to improve adherence

Near perfect adherence is necessary for maximal response to ART adherence can be improved by many types of interventions. However for these to be successful, they must become part of routine practice in the clinic.

Predictors of Adherence

A number of factors have been associated with non-adherence to ART. Understanding these factors can increase a clinician's attention to adherence when working with particularly susceptible patients and can initiate interventions to improve adherence. The factors associated with medication adherence are commonly divided into 5 intersecting categories[15].

Common predictors of non adherence

1. **Patient Variables**

   Socio-demographic factors
   - Younger age
   - Lower income
   - Lower literacy
   - Unstable housing

   Psychosocial factors
   - Depression/psychiatric morbidity
   - Active drug or alcohol use
   - Stressful life events
   - Lack of social support

   Other factors
   - Inability to correctly identify the drug regimen
   - Inability to describe the relationship between adherence and drug resistance.

   Gender, educational level and HIV risk factors generally are not associated with adherence behaviour.

2. **Treatment Regimen**
   - Complex regimen
   - High number of pills per dose
   - Medications that cause side effects
   - A regimen that does not "fi t" into an individual's daily routine

   The specifi c type of pills prescribed generally is not associated with adherence behaviour.

3. **Disease Characteristics**

Two studies describe increased adherence in those with a history of opportunistic infections. The authors postulate that experience with illness stokes the desire for health and a motivation to adhere[16-17].

4. **Patient-Provider Relationship**

- Overall dissatisfaction or mistrust in the provider or clinic staff
- Poor opinion of the provider's competence
- Provider's does not include the patient in the decision-making processes
- Relationship with provider that lacks warmth, openness, cooperation, etc
- Discordance of race/ethnicity between patient and provider
- Inadequate referrals to other sources of potential help for patients

There is also improved adherence when a patient has a longstanding and trusting relationship with a single provider. The patients' perception of being "known as a person" is signifi cantly and independently associated with receiving ART, adhering to ART, and having undetectable serum HIV RNA.

5. **Clinical Setting**

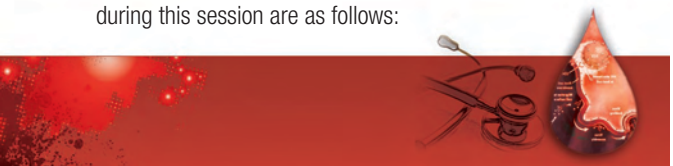
- Poor access to ongoing primary care
- Not involved in a dedicated adherence program
- In-availability of transportation
- Uncomfortable clinic environment
- Inconvenience in scheduling appointments
- Perceived lack of confi dentiality
- Dissatisfaction with prior experience in the health care system

Many factors have been associated with adherence behaviour. Some of these factors are largely not alterable by the clinician, such as the patient's socio-demographic factors. These factors can nonetheless be used by clinicians to help identify those patients at high risk for non-adherence so they can receive the most intensive adherence support. Other factors associated with non-adherence are potentially alterable, such as depression, substance abuse, homelessness, regimen complexity, medication side effects, and the therapeutic relationship between patient and provider. Alterable factors that impact adherence should be attended to, if possible, prior to starting ART, and in a proactive and ongoing way throughout therapy.

Counselling of patients starting on ART

Pre-ART counselling

Rarely is there a need to start ART urgently. Due to cross-resistance, the patient's first regime is his best option for durable viral suppression. The second regime is likely to be even more complex, and less likely to be as effective. It is helpful to have a counselling session before considering ART. The issues to consider during this session are as follows:



1. Reassess knowledge about HIV – about CD4 count, viral load etc.
2. Explain what ART is and the benefi ts of ART
3. Stress on the importance of adherence and consequences of non-adherence with regard to viral resistance. Adherence diagram for visual aid can be used for this purpose
4. Give examples of some of the common side effects so that the patient will know what to expect once he/she starts ART
5. ssess the affordability and cost of the medications and investigations (if relevant) and the cost and commitment of coming for repeated follow-ups (especially in the first few weeks after ART is initiated) to the patient
6. Assess issues in the lifestyle of the patients (e.g. occupation, frequent outstation travels, active substance abuse and odd working hours,) that can interfere with adherence
7. Help the patient identify family members or friends who can assist with and in some instances even help take responsibility for the administration of patient's medication and adherence, and those who can help him fi nancially if needed. They can then be invited to attend the second counselling session.
8. Give written material about ART
9. Consider using other PLWHA (as peer educator or 'treatment buddy') if patient has negative perceptions about ART or does not believe that the medications will work

ART Counselling

All patients must be counselled on how to take their pills. Preferably this is done after the patient has collected their medications from the pharmacy.

1. Reassess the patient's belief and perception about ART
2. Discuss with patients how the medications will fi t into their daily routines
3. Provide dosing schedule
4. Reinforce importance of adherence.
5. Consider directly observed therapy (DOT) programme with the help of a friend or family member or if patient is staying in a halfway house/centre
6. Educate about side effects
7. Schedule frequent follow-ups in the first few months.
8. Provide contact numbers, names of staffs and when they can be contacted

Counselling during subsequent clinic visits

Assessment and counselling about adherence (see below) must be an integral part of patient's clinic visits. Treatment fatigue can occur even after years of successful ART therapy. Also use positive reinforcement by sharing the viral load and CD4 cell count results and reinforce the relationship to adherence.

Assessment and counselling about adherence

Clinicians working with patients on ART need an accurate and relatively simple method of assessing adherence. It is well known that providers' estimates of adherence are inaccurate and often lead to the incorrect assumption of good adherence.

It also has been recognized that individual adherence behaviour can vary during a given period and usually deteriorates over time. A single adherence assessment provides only a snapshot of adherence behaviour. It is therefore important to reassess adherence at each visit.

Accurately assessing adherence requires clinicians to develop a collaborative and nonjudgmental relationship with patients. The key to asking patients about their adherence is taking the time to ask about adherence regularly, and doing so in an open and truly inquisitive manner. Otherwise, many patients will simply state what they believe the clinician wants to hear: that they have been perfectly adherent. The detection of non-adherence is itself a valuable accomplishment.

An abbreviated example of an Adherence Assessment Tool (adapted from *Chesney et al.*)

a) Introductory Statement

- acknowledging that difficulties taking anti-retrovirals are common
- state that the job of the clinician is to help identify these diffi culties and try to make it easier for the patient to take the medication.

b) Confi rm Understanding of Regimen

- Using a visual aid, such as a chart that shows colour images of the available antiretroviral pills, ask the patients which medications they are taking.
- For each of the indicated pills, ask how many and exactly how often they are taking them. If any answers are incorrect, clarify the regimen prior to completing the adherence assessment.

c) Assess Adherence

- Ask the patients about their adherence over the past 3 days, 1 day at a time. Start with the day prior to the interview (i.e., yesterday) and ask them how many of their pills they had missed or taken late that day. Then ask about the 2 days prior to that, addressing each day separately.
- Next, ask about how many doses they had missed or taken late over the past 7 days and 30 days. If they report no missing doses, ask them how long it has been since a dose was missed.
- Alternatively, a Visual Analogue Scale can be used to assess recent adherence using a more simple visual scale.)

d) Ask About Reasons for Missing Doses

For patients missing doses, ask them if they know the reasons why. Prompt them if they cannot offer an explanation. Common reasons why people miss medications include simply forgetting, being away from home, being too busy with other things, a schedule change, too many side effects, feeling sick or depressed, and running out of pills.

e) Ask About Medication Side Effects or Other Problems

Ask about medication side effects or other problems that they may be experiencing. Prompts can be offered, such as asking about nausea, diarrhoea, diffi culty in swallowing the pills, headaches, fatigue, depression, or any other physical or emotional complaints.

f) Collaborate with the Patient to Facilitate Adherence

- Reassure the patient that problems with adherence are common. Explain that your concern is based on the fact that missing more than 5-10% of the doses in a month (e.g., more than 3-6 doses a month in a twice-daily regimen) can lead to the treatment failure.
- Take seriously all complaints about side effects or other physical or emotional problems and address them concretely.
- Offer suggestions to overcome specifi c obstacles the patients may have mentioned, such as the use of a watch alarm, medication organizer (pill boxes), extra packages of pills at work or in the car, or an unmarked bottle for enhanced privacy. Ask the patients if they have any ideas of their own to make it easier to take the medications. Suggest placing medications in locations where they will notice them at dosing times e.g. at the breakfast table, beside the bed etc
- Finally, do not worry if the problem cannot be solved immediately; uncovering a problem with adherence is an important accomplishment and solutions to it can evolve in subsequent visits.

g) Other practical suggestions to prevent missing doses.

- Have the patient consider when medications are likely to be missed (e.g. on weekends, during visits to houses of relatives, while working overtime, when feeling unwell) and make plans to decrease these events.
- Help patients to prospectively anticipate when medicines are running out and what to do if they do run out

Adverse Events of Antiretroviral Drugs

Adverse events **(AEs)** occur with all antiretroviral agents and may be one of the reasons for switching or discontinuation of therapy and non adherence.
Differentiating between antiretroviral-related toxicities and disease complications can be difficult.
Active surveillance for clinical signs and symptoms of adverse events should be initiated during commencement of ART and during subsequent follow ups to ensure the events are carefully recorded for future reference and managed accordingly.

Principles of managing adverse events

1. Identify the adverse event and assess its possible cause: antiretroviral agents, other medications or other illnesses.
2. Assess severity of toxicities (refer **Annex 7** : Severity grading)
3. If the reaction is mild or moderate, do not discontinue ART. Implement symptomatic therapy. Counsel and monitor patients, stress the importance of adherence despite toxicity.
4. Moderate or severe toxicities may require substitution of the drug with another of the same ARV class, but with a different toxicity profi le e.g. substitution of AZT or TDF for d4T induced neuropathy, TDF or d4T for AZT associated anaemia, or NVP for EFV induced CNS toxicity or in pregnancy. (Refer **Table 6**)
5. Severe life-threatening toxicity requires discontinuation of ALL ARV drugs until the patient is stabilized and the toxicity is resolved.
6. If there is intolerance due to an individual drug, a single drug substitution can be made, however a single drug substitution should not be made if the patient is known to be biologically failing.
7. If there is a need to discontinue ART, all antiretroviral medications must be stopped together. Stopping only one drug can lead to resistance. For stopping regimes with NNRTI, refer to **'Stopping/ Interrupting NNRTI'**

Table 6 : Individual drug substitutions for toxicity and Intolerance

ARV	Frequently associated toxicity	Suggested substitute
AZT	Severe anaemia or neutropenia[1] Severe GI intolerance	TDF or d4T
	Lactic acidosis	TDF or ABC Boosted PI + NNRTI if ABC and TDF are not available (e.g. IDV/r + EFV)
d4T	Lactic acidosis Lipoatrophy /metabolic syndrome	TDF or ABC Boosted PI + NNRTI if ABC and TDF are not available (e.g. IDV/r + EFV)
	Peripheral neuropathy	AZT or TDF
TDF	Renal toxicity (renal tubular dysfunction)	AZT or d4T
EFV	Persistent and severe CNS toxicity e.g. persistent hallucinations or psychosis.	NVP
NVP	Hepatitis	EFV (except in 1st trimester of pregnancy)
	Non-severe (grade 1 or 2) moderate hypersensitivity reaction	1. EFV but careful monitoring is needed.
	Severe or life-threatening rash (Stevens–Johnson syndrome)	Stop all ARVs until stable. Then start a PI-based regimen or TDF(triple NRTI regime)[2]

Notes

1. Defi ned as neutrophil cell count <500/mm3 (grade 4)
2. Triple NRTI regimes preserve PIs for second line treatment however are inferior to PI-based regimes.

Refer **Annex 6** for a complete list of the adverse events of ARVs

Management of treatment failure: after first line treatment

Definition of treatment failure

Antiretroviral treatment failure can be defined as suboptimal response to therapy leading to loss of viral control. Treatment failure can be measured in three ways: clinically, by disease progression and WHO staging; immunologically, using trends in CD4 counts over time, and virologically, by measuring HIV viral loads (plasma HIV-1 RNA levels).

Definition of clinical failure[19]

New or recurrent WHO stage 4 condition after at least 6 months of ART.

Exceptions are lymph node TB, uncomplicated pleural TB, oesophageal candidiasis and recurrent bacterial infections; which may not always represent ART failure. When clinical events occur during the first 6 months of therapy, it is important to differentiate IRIS from treatment failure. Therefore, ART failure cannot be diagnosed based on clinical criteria alone in the first 6 months of taking ART.

Definition of immunological failure[19]

Without any concomitant infection causing transient CD4 cell count decrease, if

a) CD4 count <100 cells/mm3 (some experts recommend <50 cells/mm3) after one year of therapy; or
b) Return to or fall below the pre-therapy baseline CD4 count after therapy; or
c) 50% decline from the on-treatment peak CD4 value (if known)

Definition of virological failure[20]

This is considered the 'gold standard' indication of treatment failure. It may manifest as one of the following;

a) Incomplete virologic response: Failure to achieve HIV viral load <50 copies/ml 4–6 months after starting therapy. However it should be noted that in patients with high baseline viral-load levels the time to achieve HIV viral load <50 copies/ml may be longer or
b) Virologic rebound: After virological suppression<50copies/ml, repeated detection of HIV viral load to > 400copies/ml.

Virological failure is the most sensitive and accurate way to diagnose early treatment failure[21]. Diagnosing treatment failure based on CD4 or clinical basis alone will provide greater opportunity for the selection of drug resistance mutation before regimen change and may particularly compromise the NRTI component of the second-line regimen through incremental class-wide drug resistance.

Viral "blips"

Transient rises (4-6 weeks) in viral load to above detectable level (>50 copies/ml and <1000 copies/ml) in those who are on treatment and have achieved prior viral suppression are known as viral blips. They may reflect technical variations in laboratory assay performance, or biological events associated with viral replication (immunization, other viral infection). "Blips" are usually not associated with subsequent virologic

failure, but frequent episodes or higher viral loads, increase the risk of failure in the future. These patients should be assessed for possible causes of treatment failure. (Refer **'Initial assessment of treatment failure'**)

Initial assessment of treatment failure[22]

Most patients on potent combination therapy maintain virologic suppression for 3–7 years. However, antiretroviral treatment failure is not uncommon, and it increases the risk for HIV disease progression; therefore, it should be addressed aggressively.

The initial assessment of a patient with ARVT failure should include:

I. Thorough review of the patient's medical history:

a) change in HIV RNA and CD4 T-cell count over time
b) occurrence of HIV-related clinical events
c) antiretroviral treatment history
d) results of prior resistance testing (if any)
e) factors potentially contributing to reduced plasma drug levels such as:
   i. Poor adherence
      For incomplete adherence, identify and address the underlying cause(s) of nonadherence (e.g. access to medications, depression, active substance use), and simplify the regimen if possible (e.g. decrease pill count or dosing frequency)
   ii. Incorrect dosing/ frequency
   iii. Drug intolerance
      Management strategies for intolerance may include:
      - using symptomatic treatment (e.g., antiemetics, antidiarrheals);
      - changing one drug to another within the same drug class, if needed (e.g., change to tenofovir or abacavir for zidovudine-related gastrointestinal symptoms or anemia; change to nevirapine for efavirenz-related central nervous system symptoms)
      - changing drug classes (e.g., from an NNRTI to a PI if necessary)
   iv. Pharmacokinetics
      - Food/fasting requirements
      - Adverse drug-drug interactions with concomitant medications
f) Co morbidities (including substance use)
g) Suspected Drug Resistance:
   Obtain resistance testing (where available) while the patient is on the failing regimen or within 4 weeks after discontinuation

II. Physical examination to assess for signs of clinical progression.

General principles of changing therapy

a. Resistance develops only when there is virologic replication in the presence of antiviral pressure. Thus, poor adherence (<70 percent of prescribed doses) is associated with virologic failure but, because the selective pressure may be so low the virus may still be a sensitive to most or all of the patient's current medications. So if there is suspected inadequate adherence at the time of viral load testing , identify and address the underlying cause(s) and repeat viral load testing to reconfi rm virological failure.
b. The goal of treatment for patients with prior drug exposure and drug resistance is to re-establish maximum virologic suppression, HIV RNA <50 copies/mL .
c. The new regimen should be designed based on drug history, past and current resistance test results to identify fully active agents, and/or to use antiretroviral drugs with new mechanisms of action if available.
d. Ideally the new regimen should consists of at least 2, and preferably 3 fully active agents from at least one new class[5]
e. In general, adding a single, fully active antiretroviral drug in a new regimen is not recommended because of the risk of development of rapid resistance

When to switch

There is limited long term clinical data to guide us on the optimal time to switch therapy. The aggressive approach would be to change if patient has persistent (two values at least 1 month apart) viral load level of >400 copies/mL provided the patient is currently adherent to the regimen20. Another approach allows detectable viremia up to an arbitrary level (e.g., 1,000–5,000 copies/mL)[13 23]. If the decision to change is made too early, the months or years of further survival benefi t from any remaining antiviral activity from fi rst line drugs is lost. However if it is made too late, the effectiveness of second-line therapy may be compromised. This is because, ongoing viral replication in the presence of antiretroviral drugs promotes the selection of drug resistant mutations.

The decision should be guided by the availability of second line treatment options which are likely to suppress viral load to undetectable levels (<50 copies/ml) and which the patient is able to tolerate.

Choice of second line regimes for treatment failures

When the current fi rst line regimes based on NNRTI and 2 NRTI (usually lamivudine with AZT or d4T) fails, predicted resistance will be towards lamivudine(M184V) and NNRTIs (Y181C/I,K103N). The number of thymidine analogue mutations(TAMs) selected by AZT/d4T will depend on how long the patient is maintained on the failing regime and the viral load at the time of switch.

The recommended NRTI sequencing is based on likely resistance mutations and potential for retained antiviral activity.

Table 7 : NRTI with retained antiviral activity for second line therapy[13]

First line regime	Early switching	Delayed switching
ZDV or d4T + 3TC + NNRTI	NRTI with remaining activity	NRTI with remaining activity
	TDF, ddI – very likely ABC – likely 3TC – benefit likely	TDF, ddI – less likely ABC – unlikely 3TC – benefit less likely
TDF + 3TC/FTC + NNRTI	ZDV, d4T – very likely ddI, ABC – possible 3TC – benefit likely	ZDV, d4T – very likely ddI, ABC – unlikely 3TC – benefit less likely

Based on this the recommended second line regimes are :

Table 8 : Recommended second line regime[13]

First line	Recommended second line regime	
	NRTI	PI
AZT / d4T +3TC+NNRTI	Preferred: TDF + 3TC/FTC Alternatives: ABC+ ddI TDF + ABC	Boosted PI Crixivan + Ritonovir Lopinavir + Ritonovir Atazanavir + Ritonovir Saquinavir + Ritonovir
TDF + 3TC/FTC +NNRTI	AZT + 3TC	

Refer **Table 11** for the doses

Treatment-experienced patients with limited or no therapeutic options

For extensively treatment experienced patients with limited or no options, maintaining a CD4 above 200 becomes the main focus[24]. Viral load of up to 200 000 copies/ml may be acceptable in this group of patients[24].

If the patient is currently on therapy, continuing the failing regime* rather than stopping it has been shown to be benefi cial provided that the patient has not developed any side effects to the drugs and is clinically well[13 25-26]. This has to be balanced with the fact that there is accumulation of mutations in the long term (as early as 1 year) which may negatively impact future treatment options should they become available[27]. Hence if a potentially viable regime should become available, it must be commenced as soon as possible.

Discussion with an ID physician is strongly encouraged in the management for these patients.

***Lamivudine (3TC) may be preserved in a failing regime or added onto a salvage regime (especially in the presence of M184V mutation)[28].**

Viral resistance testing

Two types of tests can be used to assess viral resistance; Genotypic and Phenotypic testing. Genotypic assays detect drug resistance mutations present in relevant viral genes. Phenotypic assays measure the ability of a virus to grow in different concentrations of antiretroviral drugs. However both tests are prohibitively expensive and not widely available at this time. If the tests are available they should be performed in the following circumstances :

- Prior to any change in antiretroviral therapy secondary to virological failure[29].

- Prior to a change in regime for patients who have been receiving suboptimal regime including monotherapy or dual therapy in the past. Mothers who received antiretroviral therapy antenatally as part of a PMTCT regime are included in this group.

In order to optimize the accuracy of the results, testing should only be done when the viral load is > 1000 copies/ml30. Blood sampling should be done while the patient is still on therapy or within 4 weeks of stopping therapy.

Drug resistance tends to be cumulative for a given individual; thus, all prior treatment history and resistance test results should be taken into account.

HIV and co-infections

Management of Hepatitis B and HIV co-infection

Natural history of hepatitis B (HBV) infection is deleteriously affected by HIV co-infection.

Effects of HIV on HBV disease progression

1. Lower probability of spontaneous clearance of acute Hepatitis B infection
2. Higher HBV replication but lower transaminase levels in comparison with chronic HBV mono-infection
3. More rapid decline in Hepatitis B surface antibody (anti-HBs)
4. More episodes of reactivation
5. Lower seroconversion rates from HBeAg to anti-HBe antibody
6. Less necroinflammatory activity on liver biopsies but more rapid progression to liver fibrosis and cirrhosis.

Effects of ARVs on HBV

It is not uncommon to see elevations in transaminase levels after initiation of antiretroviral therapy. The rise in transaminases are due to immune restoration disease with hepatic flares and/or toxicity of antiretroviral agents.

Goals of Therapy.

1. In HBeAg positive patient:
   - Seroconversion from HBeAg to anti-HBeAb
   - Achieve a sustained suppression of HBV DNA.

2. In HBeAg negative patient:
   - Achieve a sustained suppression of HBV DNA.

Pre- treatment assessments :

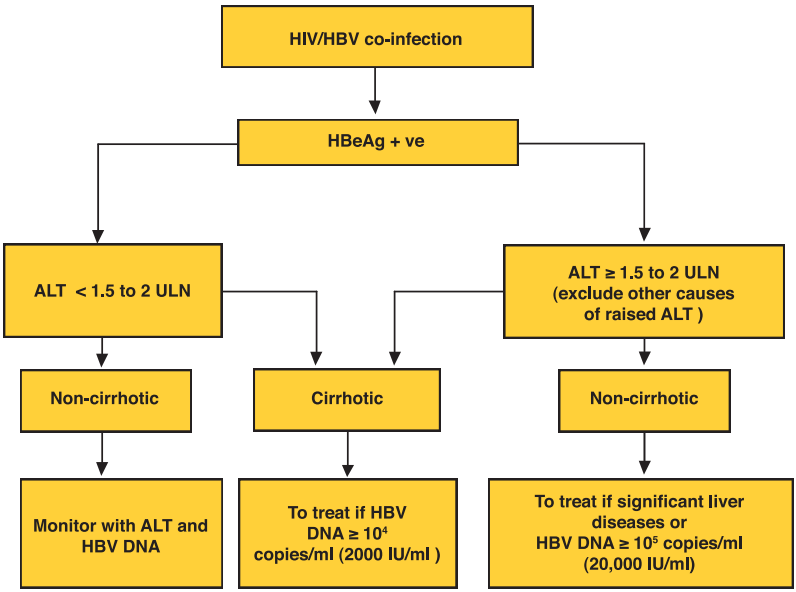
a. Full blood count , Renal profile , Liver function test , Coagulation test .
b. Serum HBeAg, anti-HBe antibody;
c. Serum HBV-DNA viral load by PCR (Quantitative)
d. Screening for other viral hepatitis infections (Hepatitis A and Hepatitis C)
e. Staging of liver fibrosis by liver biopsy, if it is deemed necessary.
f. Alfa-fetoprotein and ultrasound of liver. Consider repeating every 6-12 months in patients with liver cirrhosis, family history of hepatocellular carcinoma or those who are above 40 years old.

Treatment Recommendations for HBV and HIV co-infection

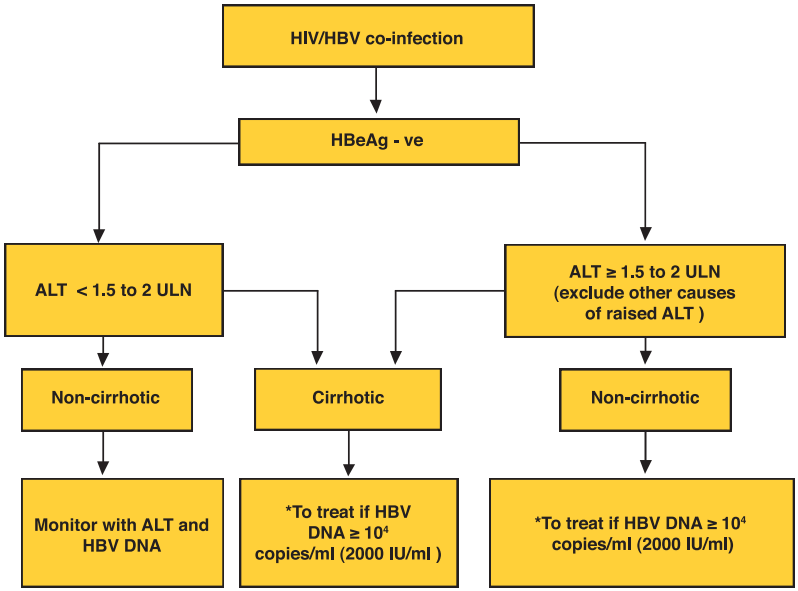
- Patients with HBV/HIV co-infection should be advised to abstain from alcohol and receive hepatitis A vaccination if the patient is not immune to it.
- It is important to monitor HBV DNA levels in patients with HBV/HIV co-infections. This is because in HBV/HIV co-infected patients, the elevations of transaminase levels do not correlate with the level of HBV replications.

- Start ART in all HIV/HBV co-infected individuals who require treatment for their HBV infection, irrespective of CD4 cell count or WHO clinical stage[13].
- Decision to treat HBV infection depends on ALT, HbeAg status, HBV DNA levels and whether patient has any evidence of liver cirrhosis. Refer algorithm 1 and 2
- Patients whose ALT 2 ULN, HBeAg negative and HBV DNA 10^4 copies/ml are unlikely to have active viral replication or active liver disease[31]. Hence, anti-HBV therapy is not recommended. However, ALT and HBV DNA need to be monitored regularly.
- Antiretroviral regime which includes two active drugs with anti-HBV action is the preferred option. The suggested ARVs regime should consist of a combination of Tenofovir and Lamivudine or Emtricitabine as the NRTI backbone[32].
- The duration of treatment for treatment of HBV / HIV co-infection is lifelong.

Algorithmn 1 : HBV treatment if HbeAg+



Algorithmn 2 : HBV treatment if HbeAg-



*HBeAg negative patients are more likely to be infected with mutant virus that prevents the expression of HBeAg even though HBV is actively replicating. Serum HBV DNA viral load of mutant viruses are at lower levels than in HBeAg positive patients and thus, they need to be treated at a lower cut off viral load (DNA 10^4 copies/ml).

Management of Hepatitis C and HIV co- infection

Introduction:

The presence of both HIV and Hepatitis C virus (HCV) will complicate the natural history of both viruses and their treatment.

Effects of HCV/HIV co-infection

HIV/HCV co-infected patients have higher HCV viral loads, more rapid progression to cirrhosis, end stage liver disease, hepatocellular carcinoma (HCC) and death[33]. In some studies, it was associated with more rapid progression to AIDS and death.

Effects of ARVs on HCV infection

HIV/HCV co-infected patients are at greater risk of anti-retroviral therapy induced hepatotoxicity, complicating efforts to treat the underlying disease[34]. On the other hand, ART slows the progression of hepatic fibrosis in co-infected patient.

Goal of treatment

The goal of HCV therapy is viral eradication or sustained virological response (SVR), an outcome associated with improved liver histology and decreased risk of progression to cirrhosis, end stage liver disease and HCC.[2] SVR is defi ned as undetectable HCV RNA (qualitative) 24 weeks after the end of therapy[35].

Pre-treatment assessment

Detection of anti-HCV antibody using 3rd generation enzyme linked immunoassay (ELISA) and Recombinant Immunoblot Assay (RIBA) method for diagnosis of HCV infection

1. HCV RNA test is recommended in patient with CD4 < 100/µL and HCV antibody negative (if HCV infection is suspected)[34].
2. HCV genotype
3. Full blood count, Renal profi le, Liver function test, Coagulation test , Antinuclear antibody, UFEME, Thyroid function test, ECG, Ultrasound of Hepatobiliary system +/- Alpha-feto protein (recommended if cirrhotic)
4. Baseline CD4 count
5. Liver biopsy to demonstrate the degree of fi brosis , if it is deemed necessary

Candidates considered for HCV treatment.

1. Non cirrhotic or Child's grade A cirrhosis
2. CD4 count > 200cells/ml
3. No underlying opportunistic infections or intercurrent infections including tuberculosis
4. No contraindications for interferon and/or Ribavirin therapy
5. Motivated patients with adequate and stable living conditions and support
6. Absence of concurrent illicit drug use
7. Signifi cant liver fi brosis on liver biopsy (if performed)

Treatment Recommendation for HCV/HIV co-infection[35]

Patients with HCV/HIV co infection should be advised to abstain from alcohol and should be given hepatitis A and B vaccines if not immune.

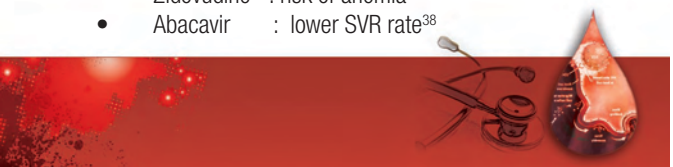
Treatment of choice:
Combination of pegylated interferon (PEG-IFN) plus weight based Ribavirin
Duration of treatment may vary from 24 to 72 weeks depending on HCV genotype. However the treatment should be discontinued if early virological response as determined by 2 log reduction of HCV viral load (as compared to baseline) is not achieved at week 12.

Preferred ART regime for patient who is a candidate for HCV therapy:

- Stavudine + Lamivudine + Efavirenz
- Tenofovir + Lamivudine+ Efavirenz
- Nevirapine can be considered in patient with baseline ALT < 2.5 times ULN

Avoid

- Didanosine : risk of mitochondrial toxicity - lactic acidosis, acute pancreatitis[36]
- Zidovudine : risk of anemia[37]
- Abacavir : lower SVR rate[38]



Management of Mycobacterium Tuberculosis and HIV Co-infection

Introduction

HIV infection signifi cantly increases the risk of progression from latent to active tuberculosis (TB) disease. Active TB, causes higher HIV viral loads and more rapid progression of HIV disease.

In HIV infected patients with drug susceptible TB infection, anti-tuberculosis treatment is as effective as in HIV negative population. Most patients are cured with the standard 6 months regime. However a longer course is needed in patients with CNS or skeletal involvement and in patients with cavitary lung disease who remain culture-positive after two months of induction therapy.

Observational studies have shown increased rates of Rifampicin resistance in patients with advanced HIV disease treated with intermittent therapy during the continuation phase. Hence for HIV-infected patients with TB who have CD4 cell counts below 100/umol/L biweekly regimes are not recommended

Management principles for scenarios seen in patients with HIV and Tuberculosis.

1. The patient is diagnosed with tuberculosis while on ART
   Continue the antiretroviral therapy. The preferred regime is 2NRTI + Efavirenz . However consult an Infectious Disease physician if the patient is on any other regimen.

2. The patient who is ART- naïve at the time of TB diagnosis
   The optimal time to initiation of ART in these patients is not known.
   The important issues to consider before initiation of ART:

   a. Risk of HIV progression if ART is delayed must be balanced with the risk of having to stop therapies because of adverse effects, paradoxical reactions and drug interactions.

   b. Drug interactions can result in sub therapeutic levels of both ART regimens and anti TB medications. This can lead to HIV virological failure and TB microbiological failure.

Table 9 : Timing of initiation of ART in HIV/TB co-infected patients[13 39]

CD4 (cells/uL)	When to start ART
<200	As soon as TB treatment is tolerated (between 2 weeks and 2 months)
200-350	After 2 months of TB treatment
> 350*	After completing 6 months TB treatment unless other WHO Clinical Stage IV conditions are present

**Regular 3 monthly CD4 count monitoring should be performed. If the CD4 count falls, patient may need to start ART.*

If the patient's CD4 count is > 350 cells/ul then the risk of HIV disease progression and death is lower. Therefore it is reasonable to complete 6 months of therapy for TB before initiation of ART. However patient's clinical condition and CD4 count has to be monitored during this period.

Preferred ART regime for patients on TB treatment:

NRTIs Options :

There are no clinically signifi cant interactions between nucleoside analog (nRTI) s and rifampicin. AZT is preferable because both d4T and ddI can cause peripheral neuropathy. This adverse effect can also be caused by Isoniazid. However, if patient cannot tolerate AZT, d4T or TDF can be used.

NNRTI Options[40] :

Efavirenz is the drug of choice because studies have shown that the virological outcomes of nevirapine based antiretroviral therapy was inferior to efavirenz based therapies. However, if the patient is already on a nevirapine based regime when diagnosed with tuberculosis, the nevirapine based therapy can be continued. The patient needs to be monitored closely for the development of hepatotoxicity.

In the event that efavirenz is intolerable due to adverse effects, nevirapine can still be used after discussion with the Infectious Disease Physician. No dosage adjustment for nevirapine is needed. The lead in dose of 200 mg daily when nevirapine is commenced is not required if rifampicin has been given for more than 1 week.

Protease Inhibitors:

Co administration of rifampicin and a protease inhibitor-based therapy is not recommended.

Antiretroviral Therapy for illicit Drug users

Antiretroviral therapy for illicit drug users

Introduction

Illicit drug users especially intravenous drug users (IDUs) often have diffi culties accessing HIV care and are less likely to receive antiretroviral therapy (ART) compared to other populations[41]. Evidence indicates that IDUs benefit significantly from HIV treatment but mortality remains high compared to non-IDUs. Factors contributing to the higher mortality include delayed initiation of treatment, poor adherence to treatment regimen, interruptions in medical care and continuing drug use.

HIV Treatment among illicit drug users/ IDUs

Available data indicates that, when not actively using drugs, effi cacy of antiretroviral therapy (ART) among IDUs is similar with other populations. Therapeutic failure in this population is generally due to the degree to which drug use results in disruption of organized daily activities, rather than drug use *per se*.

Treatment of substance abuse is often a prerequisite for successful ART[42]. Close collaboration with substance abuse treatment programs, proper support and attention to the special needs of this population with good patient–clinical team relationship are critical components of successful treatment for HIV disease.

The clinical and CD4 criteria for initiating ART in substance-dependent patients are no different from other patients.

Although not systematically studied, the apparent high incidence of drug toxicities is likely due to the high prevalence of underlying hepatic and psychiatric diseases among IDUs.

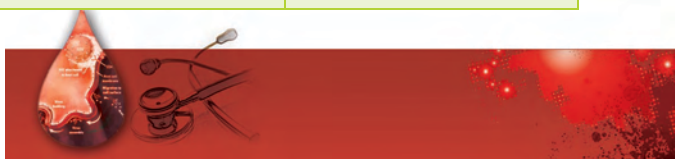
Drug Interactions

Methadone and Antiretroviral Therapy

Methadone, an orally administered long-acting opiate agonist, is the most common treatment for opiate addiction. Co-administration of NRTI, NNRTI and PIs with Methadone can result in significant alterations in methadone or ARV levels, leading to opioid withdrawal symptoms or enhanced ARVs toxicity, which may threaten ongoing adherence to therapy[43].

Table 10 : Interactions of clinical signifi cance between Methadone andART

Zidovudine (AZT)	increases the area under the curve of AZT by 40%	Watch out for marrow toxicity i.e. anaemia.
Didanosine (ddi)	Decreases levels of buffered tablet Didanosine formulation by 63%. This marked reduction in Didanosine levels is not observed with the EC formulation.	Didanosine EC formulation is preferable.



Nevirapine(NVP) Efavirenz (EFV)	Decreases in Methadone level by 46% Decreases Methadone levels by 43%	Clinical opiate withdrawal may occur, usually seen 7 days after co-administration. Adjust Methadone dosages : 5-10mg daily until patient is comfortable
Lopinavir/Ritonavir (Kaletra)	Signifi cant reduction in Methadone levels Drug interaction is attributed to Lopinavir, not Ritonavir component.	Opiate withdrawal may occur. Adjust Methadone dose accordingly.

Buprenorphine/ Subuxone (Buprenorphine/naloxone) and antiretroviral therapy

Buprenorphine and NRTIs

All NRTIs can be safely used in patient taking Buprenorphine.

Buprenorphine and NNRTIs

CYP450 3A4 inducers may decrease Buprenorphine's plasma concentration and its effi cacy. A pilot study indicates that Buprenorphine levels do not appear to be reduced and opiate withdrawal does not occur during co-administration with Efavirenz. Hence, Efavirenz is preferred to Nevirapine. If NNRTIs are used, the dosage of Buprenorphine needs to be adjusted to avoid opiod withdrawal symptoms.

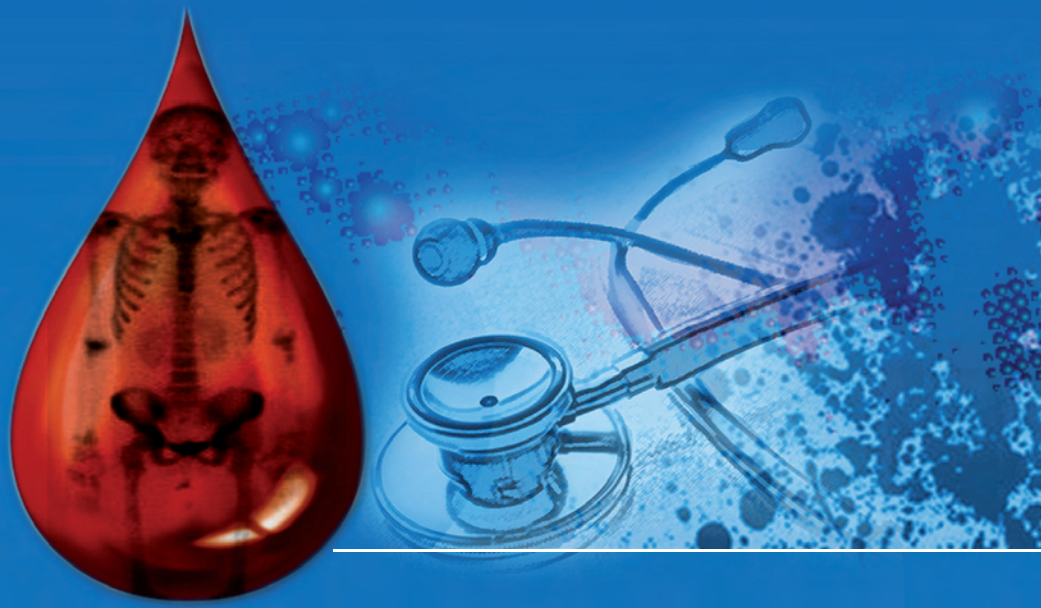
Buprenorphine and PIs

Both Indinavir and Ritonavir will enhance Buprenorphine effect by decreasing Buprenorphine metabolism. Hence, avoid using Indinavir/Ritonavir.

Subuxone (Buprenorphine/naloxone) and antiretroviral therapy

Subuxone is a popular oral substitution therapy. Limited information on drug-drug interactions is currently available.

Naloxone does not have any signifi cant drug interaction with any antiretroviral drugs. Thus, recommendations for Buprenorphine and ARVs can be applied when Subuxone is used concomitantly with ARVs



Immune Reconstitution Infl ammatory Syndrome

The immune reconstitution infl ammatory syndrome (IRIS) is a spectrum of clinical signs and symptoms resulting from the restored ability to mount an infl ammatory response associated with immune recovery[44].

It can present with:

i. signs and symptoms of a previously subclinical and unrecognized opportunistic infection, or

ii. a paradoxical worsening of treatment response several weeks into therapy, or

iii. an autoimmune disease such as Graves disease (hyperthyroidism)

Typically, IRIS occurs within two to twelve weeks after the initiation of ART, although it may present later. The incidence of IRIS is estimated to be 10% among all patients initiating ART and up to 25% among patients initiating ART with a CD4 cell count below 50 cells/mm3[45].

Risk factors predicting the likelihood of IRIS include:

I. initiating ART close to the time of diagnosis of an opportunistic infection and being antiretroviral-naive at the time of diagnosis of an opportunistic infection,

II. initiating ART when the CD4 count is below 50 cells/mm3, and

III. having a more rapid initial decrease in the HIV-1 RNA level in response to ART

The most frequently occurring IRIS events are associated with mycobacterial disease (tuberculosis or Mycobacterium avium complex infection) and cryptococcal disease. Together, these two diseases account for approximately 60% of all cases of IRIS in developed countries[46].

IRIS may be mild and resolve without treatment, e.g. it may involve a transient fl are of hepatic enzymes in a patient with HIV/hepatitis B co infection, or it may be severe and life-threatening, as in patients with cryptococcal meningitis or tuberculosis[47].

The development of a new or recurrent OI soon after ART initiation does not indicate treatment failure and is not an indication to stop or switch ART. If possible, ART should be continued and the OI or infl ammatory condition should be treated. If this is not possible, ART should be temporarily interrupted, the OI or infl ammatory condition treated, and the same ART regimen restarted at a later time.

Annexes

Annex 1: WHO clinical staging of HIV disease in adults and adolescents

CLINICAL STAGE 1
Asymptomatic Persistent generalized lymphadenopathy
CLINICAL STAGE 2
Unexplained moderate weight loss (under 10% of presumed or measured body weight) Recurrent upper respiratory tract infections (sinusitis, tonsillitis, otitis media, pharyngitis) Herpes zoster Angular cheilitis Recurrent oral ulceration Papular pruritic eruptions Seborrhoeic dermatitis Fungal nail infection
CLINICAL STAGE 3
Unexplained severe weight loss (over 10% of presumed or measured body weight) Unexplained chronic diarrhoea for longer than one month Unexplained persistent fever (intermittent or constant for longer than one month) Persistent oral candidiasis Oral hairy leukoplakia Pulmonary tuberculosis (current) Severe bacterial infections (e.g. pneumonia, empyema, pyomyositis, bone or joint infection, meningitis, bacteraemia, severe pelvic infl ammatory disease) Acute necrotizing ulcerative stomatitis, gingivitis or periodontitis Unexplained anaemia (below 8 g/dl), neutropenia (below 0.5 x 10^9/l) and/or chronic thrombocytopenia (below 50 x 10^9 /l)

CLINICAL STAGE 4
HIV wasting syndrome
Pneumocystis pneumonia
Recurrent severe bacterial pneumonia
Chronic herpes simplex infection (orolabial, genital or anorectal of more than one month's duration or visceral at any site)
Oesophageal candidiasis (or candidiasis of trachea, bronchi or lungs)
Extrapulmonary tuberculosis
Kaposi sarcoma
Cytomegalovirus infection (retinitis or infection of other organs)
Central nervous system toxoplasmosis
HIV encephalopathy
Extrapulmonary cryptococcosis including meningitis
Disseminated non-tuberculous mycobacteria infection
Progressive multifocal leukoencephalopathy
Chronic cryptosporidiosis (with diarrhoea)
Chronic isosporiasis
Disseminated mycosis (coccidiomycosis or histoplasmosis or penicilliosis*)
Recurrent non-typhoidal Salmonella bacteraemia
Lymphoma (cerebral or B cell non-Hodgkin) or other HIV-associated tumours
Invasive cervical carcinoma
Atypical disseminated leishmaniasis
Symptomatic HIV-associated nephropathy or HIV-associated cardiomyopathy

Source: Revised WHO clinical staging and immunological classifi cation of HIV and case defi nition of HIV for surveillance.2006

** added in the regional classifi cation for Asia*

Annex 2 : ARV combinations that are not recommended

Monotherapy or dual therapy	Rapid development of resistance
d4T + AZT	Antagonism (reduced levels of both drugs)
d4T + ddi	Overlapping toxicities (pancreatitis, hepatitis, lipoatrophy) Deaths reported in pregnant women
3TC + FTC	Interchangeable, but should not be used together
TDF + 3TC + ABC or TDF + 3TC + ddI	These ARV combinations will increase K65R mutation and are associated with a high incidence of early virological failure
TDF + ddI + any NNRTI	High incidence of early virological failure

Annex 3 : Dosages of Antiretroviral Drugs

Table 11 : Dosage, food interaction, storage and adjustments in hepatic insuffi ciency

Generic name	Dose
Nucleoside RTIs (NRTIs)	
Abacavir (ABC)	300 mg twice daily or 600 mg once daily Take without regard to meals Dosage adjustment in hepatic insuffi ciency[3]
Zidovudine (AZT)	250 mg or 300 mg twice daily[1] Take without regard to meals
Emtricitabine (FTC)	200 mg once daily Take without regard to meals
Didanosine (ddI) Buffered tablets(B) or enteric-coated capsules(EC)	>60 kg: 400 mg once daily <60 kg: (EC) 250 mg once daily (B) 300 mg once daily Take 1/2 hour before or 2 hours after a meal
Lamivudine (3TC)	150 mg twice daily or 300 mg once daily Take without regard to meals
Stavudine (d4T)	30 mg twice daily irrespective of weight Take without regard to meals
Nucleotide RTIs (ntRTIs)	
Tenofovir (TDF)	300 mg once daily Take without regard to meals
Non-Nucleoside RTIs (NNRTIs)	
Efavirenz (EFV)	600 mg once daily Take on an empty stomach to reduce side effects
Nevirapine (NVP)	200 mg once daily for 14 days, followed by 200 mg twice daily Take without regard to meals
Protease inhibitors (PIs)	
Atazanavir/ritonavir (ATV/r)	300 mg/100 mg once daily[2] Take with food Dosage adjustment in hepatic insuffi ciency[4]
Indinavir/ritonavir (IDV/r)	800 mg/100 mg twice daily or 600 mg/100mg twice daily Take without regard to meals Dosage adjustment in hepatic insuffi ciency

Lopinavir/ritonavir (LPV/r)	Capsule lopinavir 133.3 mg + (400/100 mg twice daily) ritonavir 33.3 mg	Three capsules twice daily (400/100 mg twice daily). If combined with EFV or NVP: Four capsules twice daily (533/133.33 mg twice daily) Take with food Refrigerate for long-term storage At room temperature: stable for 30 days
	Tablet (heat-stable formulation) lopinavir 200 mg + ritonavir 50 mg	Two tablets twice daily (400/100 mg twice daily) Take without regard to meals If combined with EFV or NVP: Lopinavir 500mg + Ritonavir 125mg twice daily(However, no LPV/r 100mg/25mg formulation is currently available in Malaysia, thus three tablets(600/150 mg) twice daily is used.
Darunavir/ritonovir (DRV/r)	600/100 mg twice daily Take with food	
Ritonavir	100 mg twice daily as booster combination Take with food if possible to improve tolerability Refrigerate for long-term storage At room temperature: stable for 30 days	

Room temperature is defined as 15–30°C. Refrigeration is defined as 2–8°C

1. AZT 250 mg 2 times per day is included as an option in the 2006 WHO guidelines for adult ART
2. If for some special reason such as intolerance to all NNRTIs, ATV is given to a treatment-naive patient; the dose is 200 mg once daily (Without RTV).
3. Abacavir : Child-Pugh Score: 5–6 = 200mg BID (use oral solution); > 6 = contraindicated
4. Atazanavir: Child-Pugh Score: 7–9 = 300mg once daily; >9 = not recommended

Annex 4 : Drug Interactions

Table 12 Drug interactions between protease inhibitors (PIs) and other drugs.

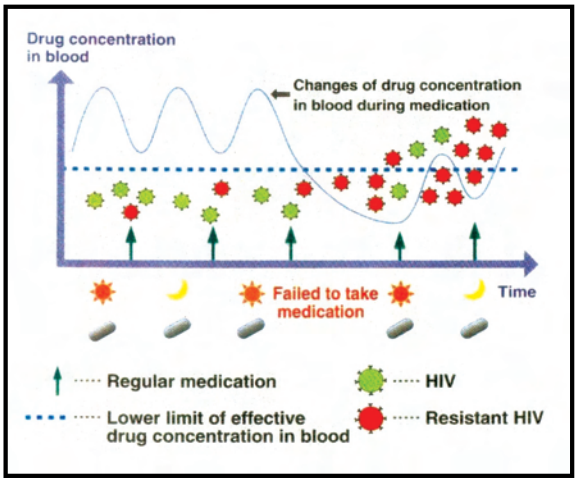
Concomitant Drug	Protease Inhibitor (PI)	Dosing recommendations and clinical comments
Acid Reducers		
Antacids	ATV/r	Give ATV/r at least 2 hrs before or 1 hr after antacids
H2 Receptor Antagonists	ATV/r	H2 receptor antagonist dose should not exceed a dose equivalent to famotidine 40mg BID in treatment-naïve patients or 20mg BID in treatment-experienced patients. ATV 300mg + RTV 100mg should be administered simultaneously with and/or >10 hours after the H2 receptor antagonist.
	DRV/r, LPV/r	No effect
Proton Pump Inhibitors (PPIs)	ATV/r	PPIs should not exceed dose equivalent to omeprazole 20mg daily in treatment-naïve patients. PPIs should be administered > 12 hrs prior to ATV/r. PPIs are not recommended in treatment-experienced patients.
Antifungal		
Fluconazole	ATV/r	No signifi cant effect
Itraconazole	ATV/r, DRV/r, IDV/r	High doses >200mg/day not recommended unless dosing is guided by drug level.
	LPV/r	Consider not exceeding 200mg itraconazole daily
Ketoconazole	ATV/r, IDV/r, DRV/r, LPV/r	Use with caution. Do not exceed 200mg ketoconazole daily
Anticonvulsants		
Carbamazepine	ATV/r, IDV/r, LPV/r	Consider alternative anticonvulsant or monitor levels of both drugs and assess virological response.
	DRV/r	Monitor anticonvulsant level and adjust dose accordingly
Lamotrigine	LPV/r	Titrate lamotrigine dose to effect. A similar interaction is possible with other RTV-boosted PI
Phenytoin	ATV/r, DRV/r, IDV/r,LPV/r	Consider alternative anticonvulsant or monitor levels of both drugs and assess virologic response. Do not co administer with LPV/r once daily.
Valproic Acid (VPA)	LPV/r	Monitor VPA levels and response. Monitor for LPV related toxicities.

Antimycobacterials		
Clarithromycin(Clar)	ATV/r	May cause QT prolongation. Reduce clarithromycin dose by 50%. Consider alternative therapy.
	DRV/r, IDV/r, LPV/r	Monitor for clarithromycin-related toxicities. Reduce clarithromycin in dose by 50% in CrCl 30-60mL/min. reduce clarithromycin dose by 75% in patient with CrCl < 30mL/min.
Rifampicin	All PIs	Do not co administer rifampicin and PIs
Benzodiazepine		
Alprazolam Diazepam	All PIs	Consider alternative benzodiazepine such as lorazepam
Lorazepam	All PIs	No data
Midazolam	All PIs	Do not co administer midazolam and PIs. Parenteral midazolam can be used with caution as a single dose and can be given in a monitored situation for procedural sedation.
Hormonal contraceptives		
Hormonal contraceptives	ATV/r	Oral contraceptive should contain at least 35mcg of ethinyl estradiol.
	DRV/r, LPV/r	Use alternative or additional method
HMG-CO A Reductase inhibitors		
Atorvastatin	All PIs	Use lowest possible starting dose with careful monitoring for toxicities or consider other HMG-Co A reductase inhibitors with less potential for interaction.
Lovastatin	All PIs	Contraindicated – do not co administer.
Pravastatin	DRV/r	Use lowest possible starting dose with careful monitoring
	LPV/r	No dosage adjustment necessary
Simvastatin	All PIs	Contraindicated – do not co administer

Interaction between PIs and Methadone: refer to ***Table 10***

Annex 5 : Tools for adherence counselling
Adherence diagram for visual aid

AIDS Clinical Centre (ACC) , International Medical Centre of Japan. November 2004.



Discussions:

The curve line indicates antiretroviral (ARV) medication levels in the blood.

The dotted line indicates “safety” level of ARV below which the ARV concentration would be too low to kill HIV viruses effectively.

Arrows indicate timing of ARV. The sun means morning dose and the moon means evening dose.

The pills represent ARV.

The green round dots represent original HIV viruses that are easily killed by ARV (wild type).

The red round dots represent HIV viruses that have already mutated to become very powerful viruses that can no longer be killed by ARV. They are like monsters.

If patient takes his ARV on time (no later than 30min from the supposed timings) without fail, his ARV level in the blood will rise with digestion and fall after being “used up”. However the level would always fall within a safety range.

This will dramatically lower the amount of HIV in patient's body.

The term viral load refers to number of viruses in 1 ml of blood. The lower the viral load, the better. For those on ARV, target viral load should be less than 50 copies/ml. However, some viruses always survive, including some with mutations.

However, even if the patient missed once or late taking ARV > 30minutes, or reduce or stop medication by self judgment, the drug concentration in blood will plunge dramatically to a dangerous level.

This would give HIV viruses a golden opportunity to fi ght back and mutate (become resistant). The resistant virus will continue to multiply and are no longer "afraid of" the ARV. Resistant mutations DO NOT disappear once they have developed!

Thus the best ARV given by the Dr. no longer works and need to consider changing to a new drug combination. Unfortunately, subsequent drug combinations most of the time are more expensive, tend to cause more adverse effects and are less tolerable. Those new drugs with similar function and structure may no longer be effective due to cross resistance.

This failure will not show any signs initially even if patient continues to miss pills. The signs will only show much later (a few months) when patient either became unwell again or when CD4 starts to drop or viral load starts to rise.

Remember!! Even if the patient misses the pill a few times, the HIV viruses may become resistant. All previous efforts (of spending money to buy ARV, tolerating side effects and trying to be adherent) would be completely wasted and the road ahead would be very diffi cult.

Visual Analogue Scale

A simple visual method of assessing adherence recently has been found to be equivalent to the more commonly used verbal self-report[48]. The Visual Analogue Scale asks subjects to indicate a point on a line that shows their best guess about how much of each drug they have taken in the past 3 or 4 weeks. For example, 0% means they have taken no drug, 50% means they have taken half their drugs, and 100% means they have taken every single dose.

In a randomised clinical trial, patient over-reporting of adherence was significantly less when asked to recall a 1-month period compared to a 3 or 7-day period recall[49].

Below is an example of a Visual Analogue Scale

Please place an "X" on the line below at the point showing your best guess about how much of your current antiretroviral medication you have taken in the **past 30 days**

0% means you have **taken none of your current antiretroviral medication, 50%** means you have **taken half** your current antiretroviral medication, **100%** means you have **taken every single dose** of your current antiretroviral medication in the past 30 days.

0%	10%	20%	30%	40%	50%	60%	70%	80%	90%	100%

Estimate percentage ……..%

Sila letak tanda "X" pada garisan di bawah untuk menunjuk peratusan ubat HIV yang dapat dimakan dalam 30 hari yang lalu.

0% bermaksud anda tidak dapat mengambil sebarang daripada ubat-ubatan anda; 50% bermaksud anda berjaya mengambil setengah daripada jumlah ubat HIV kamu; 100% bermakna kamu berjaya mengambil kesemua ubat HIV anda dalam masa 30 hari yang lalu.

0%	10%	20%	30%	40%	50%	60%	70%	80%	90%	100%

Estimate percentage ……..%

Example of a checklist for ART counselling

Bil.	Perkara	
1.	Adakah anda sudah bersedia untuk mengambil ART? Bilakah anda ingin bermula?	☐ ☐
2.	Pemeriksaan pengetahuan tentang HIV 1. HIV / AIDS 2. CD 4 3. Viral Load 4. Cara Hidup Sihat	☐ ☐ ☐ ☐
3.	Pemeriksaan pengetahuan / keterangan tentang ART 1. Berapa lama mengambil ART 2. 3 jenis ubat dan namanya 3. Regim pertama yang dicadangkan 4. Regim kedua termasuk kosnya (sekiranya regim pertama gagal) 5. Kesan kepada CD 4 & Viral Load 6. Berapa lama untuk menghasilkan / mengetahui kesan positif ART 7. Peranan ubat Bactrim atau ubat profi laksis lain	☐ ☐ ☐ ☐ ☐ ☐ ☐
4	Cadangan / Rancangan masa pengambilan ART (Jadual pengambilan) 1. Tempoh pengambilan Ubat ART (Sekali, Dua kali sehari) 2. Sesuaikan / selitkan dalam aktiviti harian / pekerjaan. 3. Sistem Pengingat (Alarm Clock/Hand Phone/pasangan) atau 4. Latihan dengan Vitamin B & C	☐ ☐ ☐ ☐
5.	Jika tertinggal / lambat mengambil ubat 1. "Virus resistant" 2. Bilangan Virus bertambah 3. Bilangan CD 4 menurun 4. Terpaksa tukar Regim (Lebih masalah; lebih kesan sampingan dan kurang effektif)	☐ ☐ ☐ ☐
6.	Kesan sampingan ART 1. 3 jenis DRUG yang dicadangkan (setiap satu) 2. Beri Pamplet Berkaitan regim 3. Buku data ART	☐ ☐ ☐
7.	Periksa dan beri 1. Masa pengambilan bersesuaian dengan cadangan / jadual 2. Beri kotak ubat 3. Cara Menyimpan Ubat 4. Buat Ujian Darah (Viral Load) sebelum mula ART	☐ ☐ ☐ ☐

NAMA KAUNSELOR.....TARIKH SESI KAUNSELING .....

Annex 6 : Adverse Events of Antiretroviral Drugs

Table 13 : Side effects and common causes

Anemia		
Associated ARV	**Comments**	**Management**
Zidovudine (AZT)	• Avoid use in patients at risk • Avoid other bone marrow suppressants if possible • Monitor FBC with differential at week-4, 8, 12 weeks (more frequently in at-risk patients)	• Stop AZT if Hb has dropped 25% of baseline/<8.0g/dL or when patient has developed symptomatic anaemia • If AZT is still required and wt < 60kg, reduce dose to 500mg daily in 2 divided doses (however increases pill burden) • If the patient is pregnant and has anaemia, consult the ID physician
Central nervous system effects		
Associated ARV	**Comments**	**Management**
Efavirenz (EFV)	Frequency - about 40% of patients. Only 3% were severe enough to justify discontinuation of EFV Symptoms : • Vivid dreams • Feeling off balance • Feels like falling over • Feels like the room is spinning • Unsteady walk • Feels like body is spinning • Feels light-headed • Feels hangover • In addition, insomnia, nightmares, mood fl uctuations, depression, depersonalization, paranoid delusion, confusion and even suicidal ideation may occur. • There is potential additive effect with alcohol and other psychoactive drugs.	• Symptoms improve with continued EFV. Rarely persist beyond 2-4 weeks. • Take at bedtime or 2–3 hours before bedtime • Avoid driving/ operating machinery or other potentially dangerous activities.

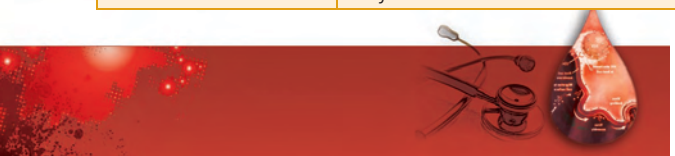
Gastrointestinal intolerance		
Associated ARVs	**Comments**	**Management**
All ARVs , Especially : Protease inhibitors (PIs) Zidovudine (AZT) Didanosine (ddi)	Symptoms : • Abdominal discomfort, loss of appetite, nausea, vomiting, heart burn, abdominal pain, constipation. • Nausea is common with AZT. • Diarrhoea is frequently seen with AZT, ddI and all PIs. • Side effects usually resolve after 4 to 6 weeks. If symptoms persist, look for other causes.	• Rule out other causes such as pancreatitis or infectious gastroenteritis. • Symptoms may spontaneously resolve or become tolerable with time. Nausea and vomiting: • Antiemetic prior to dosing • Switch to less emetogenic ARV Diarrhoea: • Antimotility agents (e.g., loperamide, diphenoxylate/ atropine) • Monitor pancreatic enzymes Severe GI symptoms: Rehydration and electrolyte replacement as indicated
Hepatotoxicity		
Associated ARVs	**Comments**	**Management**
All NNRTIs all PIs most NRTIs	NNRTI • NVP Usually occurs in the first 2-3 months of treatment. Higher risk of NVP associated hepatic AE in females with CD4 >250 cells/uL or males with CD4 >400 cells/uL at the time of initiation. NRTI Usually occurs after more than 6 months of therapy AZT , ddI , d4T Risk of hepatotoxicity associated with lactic acidosis with microvesicular or macrovesicular hepatic steatosis because of mitochondrial toxicity	Symptomatic patients: • Discontinue all ARVs and other potential hepatotoxic agents Asymptomatic patients: • If ALT >5–10x ULN, to consider discontinuing ARVs, • After serum transaminases return to normal, start a new ARV regimen without the potential offending agent(s)

	PI Usually occurs after weeks to months of treatment . Note : Indinavir : inhibits liver enzyme UDP- glucoronyl transferase thus increasing the level of bilirubin (unconjgated hyperbilirubinemia). It occurs in 7% of patients on IDV, but does not usually associated with hepatocellular injury.	
Hyperlipidemia		
Associated ARVs	**Comments**	**Management**
All PIs (except unboosted ATV); EFV > NVP d4T	NNRTIs • EFV > NVP associated with TG, LDL increase. • NNRTIs increase HDL. • Increase in TG, TC and LDL less than with PIs. NRTIs • d4T gives highest risk for TG and LDL increase. • Low or no risk with TNF and ABC PIs: • Cause elevation in total cholesterol (TC), LDL and TG. • Least or no risk: ATZ. • Usually seen within 2-3 months of starting PI.	• Lifestyle modifi cations (e.g., diet, exercise, smoking cessation) • Consider to switch to agents with less propensity for causing hyperlipidemia Pharmacologic Management: • refer to CPG on Management of Dyslipidemia Note : Refer to Annex 4: Drug Interactions for interactions between ARV and lipid-lowering agents
Hypersensitivity reaction (HRS)		
Associated ARV	**Comments**	**Management**
Abacavir (ABC)	Median onset is 9 days; approximately 90% of reactions occur within the fi rst 6 weeks Symptoms : • High fever, diffuse skin rash, malaise, nausea, headache, myalgia, chills, diarrhoea, vomiting, abdominal pain, dyspnea, arthralgia, respiratory symptoms (pharyngitis, dyspnea/ tachypnea)	• Discontinue ABC and switch to another NRTI • Rule out other causes of symptoms (e.g., intercurrent illnesses such as viral syndromes and other causes of skin rash) • signs and symptoms usually resolve 48 hours after discontinuation of ABC

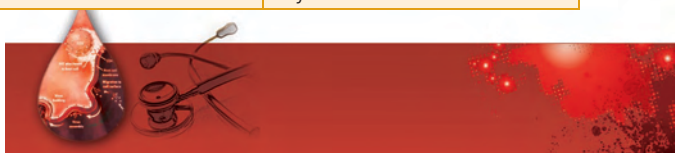
	• With continuation of ABC, symptoms may worsen to include hypotension, respiratory distress,	More severe cases: • Manage with symptomatic support (antipyretic, fl uid resuscitation, pressure support if necessary) • Do not re-challenge patients with ABC after suspected HSR, even in patients who are (-) for HLA-B*5701.
Insulin resistance / hyperglycaemia		
Protease inhibitors (PIs) Others : AZT, ddi	It occurs weeks to months after beginning of therapy	Diet and exercise Consider to switch to NNRTI if feasible Consider switching to non-thymidine analog-containing ARVs Pharmacotherapy : Refer to *CPG on Management of DM*
Lactate : Hyperlactatemia /Lactic acidosis		
Associated ARVs	**Comments**	**Management**
d4T > ddI > AZT > other NRTIs. *Note :Venous blood sampling should be done without tourniquet. Blood needs to be collected in a pre-cooled fluoride oxalate tube, transported to lab on ice immediately and lactate level measured within 4 hours*	3 Clinical syndromes : a) lactic acidosis with hepatic steatosis b) symptomatic lactatemia without acidosis / liver failure c) asymptomatic lactatemia Symptoms : • Nonspecifi c GI prodrome (nausea, anorexia, abdominal pain, vomiting), weight loss, and fatigue • Subsequent symptoms : tachycardia, tachypnea, hyperventilation, jaundice, muscular weakness, mental status changes, or respiratory distress • May present with multi-organ failure (e.g., hepatic failure, acute pancreatitis, encephalopathy, and respiratory failure)	Lactate 2-5 mmol/L but asymptomatic: Observe. Note - Do not measure lactate unless symptomatic Lactate 2-5mmol/L + symptoms ± Liver abnormality: Stop ARVs Lactate> 5mmo/L Or lactatic acidosis : • Stop ARVs • Exclude other precipitating factors • Intensive care support • To consider : IV thiamine and/or ribofl avin / bicarbonate infusions / haemodialysis

	• typically present after several months of therapy • Risk & severity increases with time on treatment (usually takes months / years) but sometimes can occur soon after starting Rx *Note :The half-life of mitochondrial DNA ranges from 4.5 to 8 weeks and hence the time required for clinical recovery after stopping NRTI is 4 to 8 weeks*	ARV treatment options: Use NRTIs with less propensity for mitochondrial toxicity (ABC, TDF, 3TC,) Recommend close monitoring of serum lactate after restarting NRTIs Consider NRTI-sparing regimen if severe / recurrent lactic acidosis
Lipodystrophy		
Associated ARVs	**Comments**	
d4T> AZT>other NRTI	Fat wasting (lipoatrophy): face, arms, leg, buttocks Fat accumulation: Abdomen, neck, gynaecomastia , buffalo hump, multiple lipomas, Cushingoid appearance without Cushing's disease.	Switch from thymidine analogs to TDF or ABC, which may slow or halt progression but may not fully reverse effects Surgical options provide cosmetic improvement : Lipoatrophy: Facial fi lling with collagen, synthetic polymers or silicone Lipodystrophy: Liposuction
Nephrolithiasis / urolithiasis / crystalluria		
Associated ARV	**Comments**	**Management**
Indinavir (IDV)	It can occur any time after beginning of therapy, especially at times of reduced fl uid intake	Prevention : Drink at least 1.5–2 litres of non-caffeinated fluid (preferably water) per day Treatment : Increase hydration: Increase fl uid intake at fi rst sign of darkened urine Switch to alternative agent Refer to Urologists when indicated

Neuromuscular weakness syndrome (ascending)		
Associated drugs	**Comments**	**Management**
D4T > other NRTIs	It occurs after months of ARV. Symptoms: Very rapidly progressive ascending demyelinating polyneuropathy, may mimic Guillain-Barré syndrome	Discontinue ARVs Supportive care, including mechanical ventilation if needed Other measures include plasmapheresis, high-dose corticosteroids, intravenous immunoglobulin, carnitine, acetylcarnitine Recovery often takes months and ranges from complete recovery to substantial residual defi cits; symptoms may be irreversible in some patients Do not re-challenge patient with offending agent.
Pancreatitis		
Associated ARVs	**Comments**	**Management**
ddI alone; ddI + d4T, ddi + TDF Note: Do not use ddI in patients with history of pancreatitis Avoid concomitant use of ddI with d4T, TDF, Reduce ddI dose if need to be used with TDF	ddI alone: 1%–7% ddI with d4T or TDF : frequency	Discontinue offending agent(s) Manage symptoms of pancreatitis (bowel rest, IV hydration, pain control, then gradual resumption of oral intake) Parenteral nutrition may be necessary in patients with recurrent symptoms upon resumption of oral intake
Periphery neuropathy		
Associated ARVs	**Comments**	**Management**
d4T > ddi	It occurs weeks or months after initiating therapy Usually presents with a distal symmetrical distribution and sensorimotor paralysis. Non-drug related risk factors: lower baseline CD4 count, history of non-drug associated peripheral neuropathy, age > 40 years	Discontinue offending agent may halt further progression, but symptoms may be irreversible May consider to substitute alternative ARV without potential for neuropathy Avoid tight shoes or long periods of standing and walking.



	Note : HIV associated polyneuropathy does not worsen and may improve with prolonged ARV treatment .	Cold showers before bed may relieve pain Pharmacologic management • Vitamin B supplement • Analgesics : Ibuprofen, Paracetamol, Tramadol • Gabapentin • Antidepressants : amitriptyline • Anticonvulsants : lamotrigine, carbamazepine • Tramadol • Narcotic analgesics • Topical capsaicin • Topical lidocaine **Note :** Symptoms frequently improve within the first 2 months following the discontinuation of the offending drug but may initially increase in intensity ('coasting') and are not always fully reversible.
Rashes		
Associated ARV	**Comments**	**Management**
Nevirapine (NVP)	Rash is greatest in the first 6 weeks of treatment. Constitutional symptoms : • Fever> 37 ºC • Blistering • Oral lesions • Conjuctivitis • Signifi cant elevations in LFTs • Facial oedema • Myalgia/arthralgia • Generalized malaise	In the presence of mild to moderate rash without constitutional symptoms or biochemical hepatitis, the lead-in (200mg od) dose may be continued without dose escalation until rash resolution, but no longer than 28 days total. However, the drug should be permanently discontinued if constitutional symptoms are present, the rash is severe or hepatitis is present. Also refer: **Stopping / Interrupting NNRTI** If NVP is interrupted for > 7days, reintroduce with 200mg/ day lead-in.



Stevens-Johnson syndrome (SJS) / toxic epidermal necrosis (TEN)		
Associated ARVs	**Comments**	**Management**
NVP>EFV Others : ABC , AZT , IDV, LPV/r , ATV , DRV	Incidence : NVP: 0.3%–1% EFV: 0.1% ABC, ZDV, IDV, LPV/r, ATV, DRV: 1–2 case reports	• Discontinue all ARVs and any other possible agent(s) • Do not re-challenge with offending drugs • Aggressive symptomatic support

Annex 7 : Severity grading

Source: Division of AIDS, National Institute of Allergy and Infectious Diseases, USA – modifi ed

GRADE 1 Transient or mild discomfort; no limitation of activity; no medical intervention/therapy required.

GRADE 2 Mild to moderate limitation of activity; some assistance may be needed; no or minimal medical intervention/therapy required.

GRADE 3 Marked limitation of activity; some assistance usually required; medical intervention / therapy required; hospitalization possible.

GRADE 4 Extreme limitation of activity; signifi cant assistance required; signifi cant medical intervention/ therapy required; hospitalization or hospice care.

	Grade 1	Grade 2	Grade 3	Grade 4
Haemoglobin	8.0 – 9.4 g/dl	7.0 – 7.9 g/dl	6.5 – 6.9 g/dl	<6.5 g/dl
Hyperbilirubinaemia	>1.0 – 1.5 x ULN	>1.5 – 2.5 x ULN	>2.5 – 5 x ULN	>5 x ULN
TRANSAMINASES				
AST (SGOT)	1.25 – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 10.0 x ULN	>10.0 x ULN
ALT (SGPT)	1.25 – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 10.0 x ULN	>10.0 x ULN
GGT	1.25 – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 10.0 x ULN	>10.0 x ULN
Alkaline Phosphatase (ALP)	1.25 – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 10.0 x ULN	>10.0 x ULN
Lactate	<2.0 x ULN without acidosis	>2.0 x ULN without acidosis	Increased lactate with pH <7.3 without life- threatening consequences	Increased lactate with pH <7.3 with life threatening consequences
Amylase	>1.0 – 1.5 x ULN	>1.5 – 2.0 x ULN	>2.0 – 5.0 x ULN	>5.0 x ULN
Lipase	>1.0 – 1.5 x ULN	>1.5 – 2.0 x ULN	>2.0 – 5.0 x ULN	>5.0 x ULN
Creatinine	>1.0 – 1.5 x ULN	>1.5 – 3.0 x ULN	>3.0 – 6.0 x ULN	>6.0 x ULN

Tables

**For table 1 – 13, please refer to the page mentioned*

Table 14 : Dosage adjustment for ART in renal impairment

Drug adjustments are based on patient's estimated creatinine clearance, which can be calculated as:

Female: Clearance (ml/min) = (1.04 x (140-age) x weight (kg)) ÷ creatinine (µmol/l)
Male: Clearance (ml/min) =(1.23 x (140-age) x weight (kg)) ÷ creatinine (µmol/l)

ART	ADJUSTMENT FOR RENAL FAILURE (CrcI)Ml/MIN			HEMODIALYSIS, CAPD	COMMENTS & DOSAGE FOR CRRT
	>50 - 90	10 – 50	<10		
LAMIVUDINE	300MG q24h	50-150MGq24h	25-50MG q24h	HEMO: Dose AD; CAPD: No Data; CRRT: 100mg 1ST day, THEN 50mg/day	
MARAVIROC	300mg bid	No data	No data	Increased risk of side effects if maraviroc+CYP3A inhibitor and CrCl<50	
STAVUDINE	100%	50%q12-24h Same dose for CRRT	>60kg:20mg/ day, <60kg:15mg/ day.	Hemo: DOSAGE as for CrCl<10 ; AD CAPD: no data	CRRT: full dose
TENOFOVIR	300mg q24h	300mg every 48 H	300mg every 72-96h	Every 7 days after the dialysis	
ZIDOVUDINE	300mg q12h	300mg q12h Same dose for CRRT	100mg q6-8h	Hemo: Dose for CrCl<10 CAPD: Dose for CrCl<10	

AD: after dialysis; **Hemo:** Haemodialysis; **CAPD:** chronic ambulatory peritoneal dialysis; **ESRF:** End stage renal failure

List of ARVs with no dosage adjustment with renal insuffi ciency

Efavirenz	Darunavir
Abacavir	Saquinavir
Atazanavir	Indinavir
Lopinavir	Raltigravir

Table 15 : Drug interactions between NNRTIs and other drugs.

Concomitant Drug class/ Name	NNRTI	Dosing recommendations and clinical Comment
Antifungals		
Fluconazole	EFV	No signifi cant effect
	NVP	Increased risk of hepatotoxicity possible with this combination. Monitor NVP toxicity or use alternative antiretroviral agent.
Itraconazole	EFV	Dose adjustment for itraconazole may be necessary. Monitor itraconazole level.
	NVP	Consider monitoring itraconazole and NNRTI level.
Ketoconazole	NVP	Co administration is not recommended.
Anticonvalsants		
Carbamazepine Phenytoin	EFV	Monitor anticonvalsant and EFV levels, or possible, use alternative anticonvalsant
	NVP	Monitor anticonvulsant and NVP levels and virologic response.
Anti mycobacterials		
Clarithromycin	EFV, NVP	Monitor for effi cacy or consider alternative agents such as azithromycin, for MAC treatment.
Rifampicin	EFV	Maintain EFV 600mg once daily and monitor for virologic response.
Benzodiazepines		
Alprazolam	EFV, NVP	Monitor for therapeutic effi cacy of alprazolam
Lorazepam	EFV	No dosage adjustment necessary.
Midazolam	EFV	Do not co administer with oral midazolam. Parenteral midazolam can be used with caution as a single dose and can be given in a monitored situation for procedural sedation.
Hormonal contraceptives		
Hormonal contraceptives	NVP	Use alternative or additional methods
HMG- Co A reductase inhibitors		
Atorvastatin	EFV, NVP	Adjust statins according to lipid response, not to exceed the maximum recommended dose.
Lovastatin, Simvastatin	EFV, NVP	
Pravastatin	EFV	
Oral anticoagulant		
Warfarin	EFV, NPV	Monitor INR and adjust warfarin accordingly

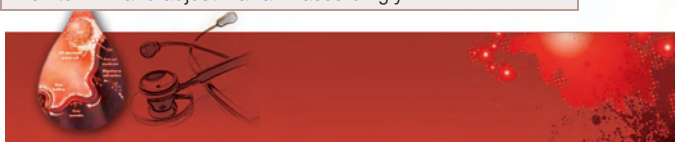


Table 16 : Drug interactions between NRTIs and other drugs

Antiviral		
Gancyclovir	ddI	Monitor for ddI associated toxicities.
Ribavirin	ddI	Contraindicated- do not co administer. Fatal hepatic failure and other ddI-related toxicities reported with co administration.
	AZT	Avoid co administration if possible or closely monitor virologic response and hematotoxiciy
Others		
Allopurinol	ddI	Contraindicated- do not co administer. Potential for increased ddI associated toxicities

Interaction between NRTIs, NNRTIs and Methadone: refer to **Table 10**

Table 17 : NRTI and common adverse events

Drug	Adverse events
Abacavir (ABC)	• Hypersensitivity reaction symptoms* may include fever, rash, nausea, vomiting, malaise or fatigue, or respiratory symptoms such as sore throat, cough, or shortness of breath.
Didanosine (ddi)	• Pancreatitis • Peripheral neuropathy • Lactic acidosis with hepatic steatosis (rare but potentially life-threatening toxicity) • Potential association with noncirrhotic portal hypertension
Lamivudine (3TC)	• Minimal toxicity • Severe acute exacerbation of hepatitis may occur in HBV-coinfected patients who discontinue 3TC.
Stavudine (d4T)	• Peripheral neuropathy • Lipoatrophy • Pancreatitis • Lactic acidosis with hepatic steatosis (rare but potentially life-threatening toxicity) • Hyperlipidemia • Rapidly progressive ascending neuromuscular weakness (rare)
Tenofovir (TDF)	• Asthenia, headache, diarrhoea, nausea, vomiting, and fl atulence • Renal insuffi ciency †, Fanconi syndrome • Osteomalacia • Potential for decrease in bone mineral density • Severe acute exacerbation of hepatitis may occur in HBV-coinfected patients who discontinue TDF
Zidovudine (AZT)	• Bone marrow suppression: macrocytic anemia or neutropenia • Gastrointestinal intolerance, headache, insomnia, asthenia • Nail pigmentation • Lactic acidosis with hepatic steatosis (rare but potentially life-threatening toxicity)

* Can occur at any time but usually in the fi rst 6 weeks of treatment
Should not be re-challenged following a hypersensitivity reaction

† Renal tubular damage has been reported but risk of serious renal damage is 0.5%

Table 18 : NNRTI and common adverse events

Drug	AE
Efavirenz (EFV)	• Rash* • Central nervous system symptoms† • Increased transaminase levels • Painful gynecomastia • False-positive results reported with some cannabinoid and benzodiazepine screening assays • Teratogenic in nonhuman primate and potentially teratogenic in humans
Nevirapine (NVP)	• Rash, including Stevens-Johnson syndrome* • Symptomatic hepatitis, including fatal hepatic necrosis, has been reported

*During clinical trials, NNRTI was discontinued because of rash among 7% of NVP-treated, 1.7% of EFV-treated patients. Rare cases of Stevens-Johnson syndrome have been reported with all NNRTIs; the highest incidence was seen with NVP.

† Adverse events can include dizziness, somnolence, insomnia, abnormal dreams, confusion, abnormal thinking, impaired concentration, amnesia, agitation, depersonalization, hallucinations, and euphoria. Overall frequency of any of these symptoms associated with use of efavirenz was 52% compared with 26% among controls subjects; 2.6% of those persons on EFV discontinued the drug because of these symptoms. Symptoms usually subside spontaneously after 2–4 weeks.
Hence, it is recommended to be taken in the evening during fi rst few weeks of starting therapy to reduce the side effect. However this does not eliminate it due to its long t½ (36-100 hr).

Table 19 : Protease inhibitors and common adverse events

Drug	AE
Atazanavir (ATZ)	• Indirect hyperbilirubinemia • Prolonged PR interval—fi rst degree symptomatic AV block in some pts • Use with caution in pts with underlying conduction defects or on concomitant medications that can cause PR prolongation • Hyperglycemia • Fat maldistribution • Possible increased bleeding episodes in patients with hemophilia • Nephrolithiasis
Darunavir (DRV)	• Skin rash (10%)—DRV has a sulfonamide moiety; Stevens-Johnson syndrome and erythrema multiforme have been reported • Hepatotoxicity • Diarrhoea, nausea • Headache • Hyperlipidemia • Transaminase elevation • Hyperglycemia • Fat maldistribution • Possible increased bleeding episodes in pts with hemophilia
Indinavir (IDV)	• Nephrolithiasis • GI intolerance, nausea • Indirect hyperbilirubinemia • Hyperlipidemia • Headache, asthenia, blurred vision, dizziness, rash, metallic taste, thrombocytopenia, alopecia, and hemolytic anemia • Hyperglycemia • Fat maldistribution • Possible increase
Lopinavir/Ritonavir (Kaletra-LPV/r)	• GI intolerance, nausea, vomiting, diarrhoea • Asthenia • Hyperlipidemia (especially hypertriglyceridemia) • Elevated serum transaminases • Hyperglycemia • Fat maldistribution • Possible increased bleeding episodes in pts with hemophilia • PR interval prolongation • QT interval prolongation and torsade de pointes

Ritonavir (RTV)	• GI intolerance, nausea, vomiting, diarrhoea • Paresthesias — circumoral and extremities • Hyperlipidemia (especially hypertriglyceridemia) • Hepatitis • Asthenia • Taste perversion • Hyperglycemia • Fat maldistribution • Possible increased bleeding episodes in pts with hemophilia
Saquinavir (SQV)	• GI intolerance, nausea, and diarrhoea • Headache • Elevated transaminase enzymes • Hyperlipidemia • Hyperglycemia • Fat maldistribution • Possible increased bleeding episodes in pts with hemophilia

Tables 3-7 adopted from DHHF guideline 2009

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LIST OF ABBREVIATIONS

3TC	lamivudine
ABC	abacavir
ART	antiretroviral therapy
ARV	antiretroviral drug
ATV	atazanavir
AZT	zidovudine (also known as ZDV)
bPI	boosted protease inhibitor
CD4	T-lymphocyte bearing CD4+ receptor
d4T	stavudine
ddI	didanosine
EFV	efavirenz
FBC	full blood count
FDC	fixed-dose combination
FTC	emtricitabine
HIV	human immunodefi ciency virus
HBV	hepatitis B virus
IRIS	immune reconstitution infl ammatory syndrome
LPV	lopinavir
NNRTI	non-nucleoside reverse transcriptase inhibitor
NRTI	nucleoside reverse transcriptase inhibitor
NVP	nevirapine
PI	protease inhibitor
RTV	ritonavir
TB	tuberculosis
TDF	tenofovir disoproxil fumarate
VL	viral load

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