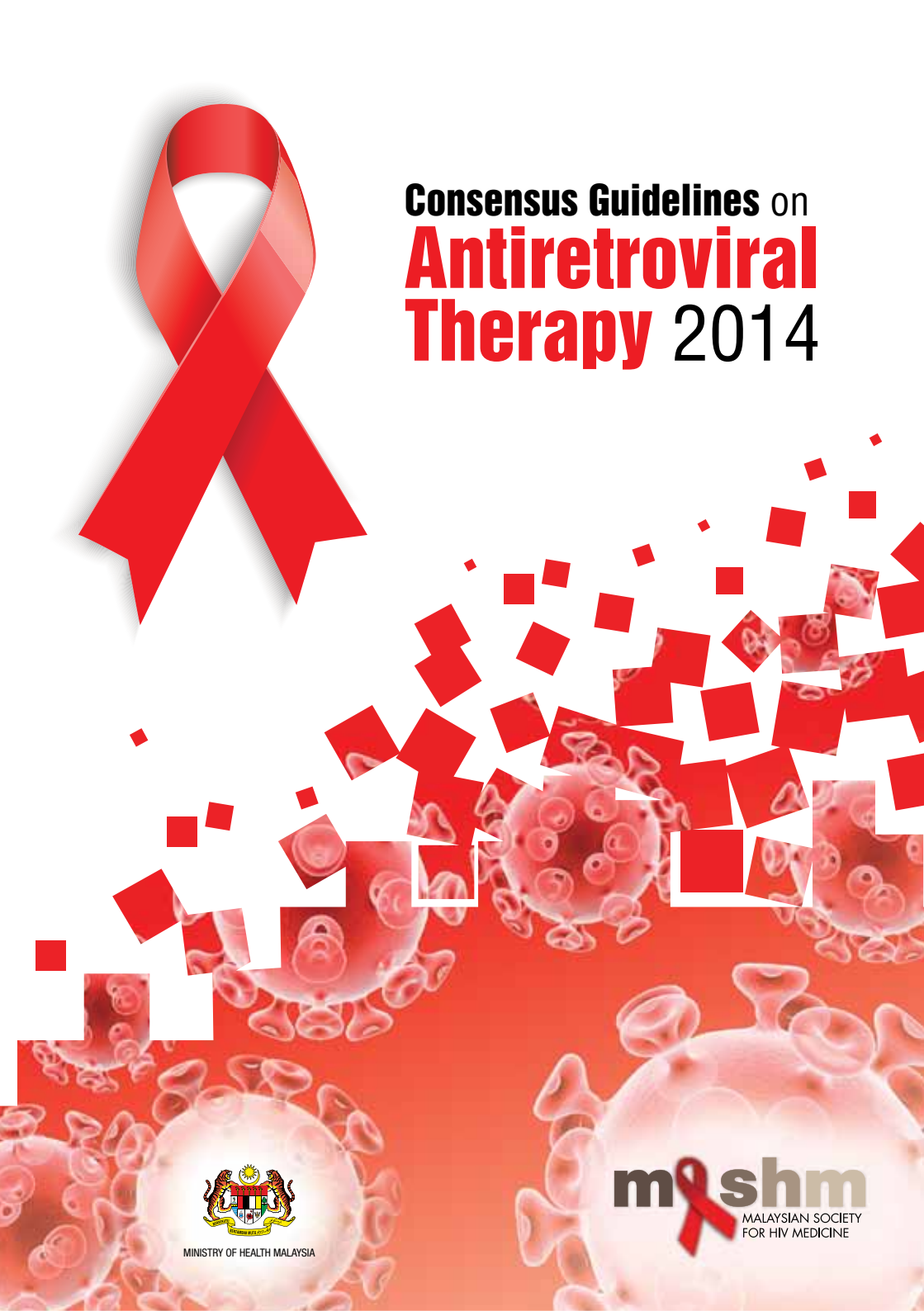
Consensus Guidelines on Antiretroviral Therapy 2014



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INTRODUCTION

The treatment of Human Immune Deficiency Virus (HIV) has been revolutionized by new potent combination of highly active antiretroviral drugs (HAART) since 1996. ART (antiretroviral therapy) has dramatically reduced HIV-associated morbidity and mortality and has transformed HIV disease into a chronic, manageable condition. Widespread use of potent ART has effectively reduced opportunistic infection-related mortality among HIV-infected persons, improving quality of life and survival.

The primary goal of this guideline is to provide HIV care practitioners with recommendations based on current knowledge of antiretroviral drugs (ARV) used to treat HIV-infected adults in Malaysia. Clinical decisions regarding starting ART in HIV affected individuals should be tailored according to patients' circumstances.

Following are Few Factors that Need To Be Taken into Consideration When Initiating ART:

1. Patient's willingness to start and adhere strictly to treatment and follow up
2 Patient's understanding of the possible adverse effects and the risk of immune reconstitution syndrome
3. The ART options that are available
4. Underlying medical diseases eg cardiovascular disease, diabetes mellitus, hyperlipidaemia, depression etc
5. Possible drug-drug interactions, dosing frequency and pill burden
6. Risk of primary resistance eg acquisition of HIV from a partner who is already on treatment
7. Individual factors that may hinder adherence eg irregular working hours, social support etc

Goals And Benefits of Antiretroviral Therapy

Highly Active Antiretroviral Therapy (HAART) is a potent combination of three or more active anti-retroviral drugs (ARV). ARVs are unable to eradicate HIV virus or cure HIV infection. The primary goals of initiating HAART are to:

1. Reduce HIV related morbidity and mortality
2. Improve quality of life
3. Increase lifespan[1,2]
4. Restore and preserve immunologic function
5. Maximally and durably suppress viral load (i.e. to undetectable plasma HIV RNA)
6. Reduction in complications associated with HIV / AIDS eg wasting syndrome, AIDS dementia and encephalopathy
7. Prevent HIV transmission to uninfected sexual partner and the unborn child
8. Prevent emergence of HIV drug resistance

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2. Wood E; Low–Beer, S; Batholomew K, et al."Modern antiretroviral therapy improves life expectancy of gay and bisexual in Vancouver's West End". *Canadian Journal Of Public Health*. March 2000;91:125-8

Treatment outcomes may be measured from three aspects:

1. Clinically by reduction in the number and frequency of opportunistic infections and improvement of general wellbeing
2. Immunologically by gradual and steady rise in CD4 T cell counts
3. Virologically by a decrease in viral load, ideally to undetectable level at six months after initiation of treatment

ART in Malaysia

Antiretroviral treatment options have expanded greatly since the first drug, zidovudine was approved in 1987. Currently, there are six classes of anti-retroviral agents which target different phases in the HIV life cycle (Table 1).

Table 1 • ARVs that are Registered in Malaysia

1. Nucleoside Reverse Transcriptase Inhibitors (NRTI) / Nucleotide Reverse Transcriptase Inhibitors (ntRTI)

Abacavir (ABC)
Didanosine buffered or enteric coated (DDI)
Emtricitabine (FTC) (available as combination pill)
Lamivudine (3TC)
Stavudine (D4T)
Tenofovir (TDF)
Zidovudine (AZT)

2. Non-Nucleoside Reverse Transcriptase Inhibitor (NNRTI)

Efavirenz (EFV)
Etravirine (ETV)
Nevirapine (NVP)

3. Protease Inhibitors (PI)

Atazanavir (ATV)
Darunavir (DRV)
Lopinavir / ritonavir (LPV/r)
Ritonavir (RTV)
Saquinavir (SQV)

4. Integrase Inhibitors

Raltegravir

5. CCR5 Antagonist

Maraviroc

6. Fusion Inhibitor

Enfuvirtide

Fixed Dose Combination

Fixed dose combination (FDC) is a combination of two or more active drugs in a single pill. FDC reduce the pill burden and associated cost. It enables the physician to prescribe the most effective dosages according to published data. Dosing simplification will improve adherence and maintain durable virological suppression.[1, 2]

Table 2 • Fixed Dose Combinations Registered in Malaysia

Abacavir / lamivudine
Tenofovir / emtricitabine
Zidovudine / lamivudine
Stavudine / lamivudine / nevirapine (SLN)
Abacavir / lamivudine / zidovudine (Trizivir)
Zidovudine / lamivudine / nevirapine

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Assessment of Adults with HIV Infection

i. Initial assessment and management of newly diagnosed patients.

All adults with HIV infection should have a complete history, physical examination, baseline laboratory evaluation and counseling about the HIV infection.

The aims and objectives of the initial assessment are:

1. To confirm the diagnosis of HIV infection
2. To ensure patient understands HIV infection and its mode of transmission
3. To obtain appropriate baseline historical and laboratory data
4. To look for evidence of opportunistic infections or HIV-related illnesses
5. To initiate care[1]

For treatment-experienced patients who present for evaluation to a new health care provider, it is important to obtain a complete antiretroviral (ARV) history, preferably by the reviewing of past medical records[2]

Newly diagnosed patients should also be asked about any prior use of ARV agents for prevention of HIV infection (pre and post-exposure prophylaxis)[2]

i. A thorough history is mandatory for all patients with HIV infection.

Table 3 • History Taking for a HIV Positive Patient[3]

	Symptoms / Components	Significance
History of Presenting Complaint	Fever, Cough, Dyspneoa, Diarrheoa, constitutional symptoms. Lethargy, weakness, weight loss loss, forgetfulness.	Diagnosis of opportunistic infections. Symptoms of AIDS
Drug History	Current medications & dosage Alternative medications Smoking & Alcohol Recreational drugs use Drug addiction	Allergy Potential drug interaction Route: IV, oral etc.
Past & Current Medical History	TB, hepatitis, herpes, varicella, STI (Syphilis, gonorrheoa, Chlamydia) DM, IHD, HPT, Renal disorder, Dyslipidaemia. Treatment received or completed for the above. Vaccinations Last negative HIV test.	Risk of worsening of preexisting condition due to ARVs.

	Symptoms / Components	Significance
Psychosocial History	Circle of confidentiality Partner & Children Support network Occupation, housing, mental health issues	
Sexual & Reproductive History	Sexual history & practices Safer sex & risk reduction Partner status & disclosure Conception issue	PMTCT prophylaxis. Transmission prevention measures.

ii. **A complete physical examination is mandatory for ALL patients with HIV to look for signs related to AIDS and opportunistic infections.**

iii. **Laboratory testing for initial evaluation AND monitoring during follow-up.**

Table 4 • Important Laboratory Investigations

Evaluation	Investigations	Specific Tests	Entry to Care	Pre-HAART	At Follow-up on HAART	Comments
HIV Disease	All referred cases of HIV infection need a confirmatory test.					
	Plasma HIV RNA	HIV viral load	See comment	x	Every 4 to 6 months after initiation of ART. Every 6 to 12 months if stable.	Not for routine baseline if resources are limited.
	CD4 (+/- %)		√	√	Every 4-6 months. Every 6 to 12 months.	After starting HAART Once stable on treatment
Co-infections	Syphilis serology	VDRL/RPR/TPHA	√	X	Annual screening if at risk	Consider more frequent screening if at risk.
	Chlamydia & Gonorrhoea	Urine (first-void) NAAT for gonorrhoea & Chlamydia	√	X		
	Hep B Serology	Hep. Bs Ag (HbsAg) Anti-Hep. Bs (HbsAb)	√	X	Annual screening if at risk	Vaccinate if non-immune. Consider testing for Anti-Hep B core (HBc Ab total) if Hep Bs Ag negative and liver function abnormal.
	Hep C Serology	HCV Antibody	√	X	Annual screening if at risk	Measure HCV RNA if HCV antibody positive or acute infection suspected.
CXR			√	X	When clinically indicated	To look for active TB (consideration for IPT).

Evaluation	Investigations	Specific Tests	Entry to Care	Pre-HAART	At Follow-up on HAART	Comments
Co-morbidities						
Hematology	FBC		√	√	Every 4 to 6 months	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 or if symptomatic
CVS	ECG		√ See comments	If on PIs	When clinically indicated.	If patient has other risk factors for IHD
Metabolic	Fasting lipid profile	TC, HDL, LDL, TG	√	X	Every 6 to 12 months	EFV, NRTIs, PIs (with the exception of unboosted atazanavir), can cause insulin resistance and dyslipidaemia.
	Glucose	FBS & HbA_{1c}	√	X		
Liver	ALP, AST ALT, Bilirubin, Albumin		√	√	Every 4 to 6 months	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
Renal	Renal function test/ eGFR		√	√	Every 6 months If patient is on TDF, 4-8 weeks post ART initiation and then every 4 to 6 months	TDF may cause renal tubular dysfunction Routine monitoring of calculated creatinine clearance should be performed for all patients on TDF during follow up
Urinalysis	Dipstick		√	As clinically indicated		
Others	Serum Lactate		X	X	As clinically indicated	Lactic acidosis is a rare but severe complication of NRTI therapy caused by mitochondrial dysfunction. The risk is highest in regimens containing d4T
	Pregnancy test	Urine Pregnancy test (UPT)	When clinically indicated			To identify women who need ART as treatment for prevention or ARV prophylaxis for PMTCT
	Pap smear for women	Pap smear	Annually			

Monitoring While on Antiretroviral Therapy (see Table 4)

CD4 Count:

Successful therapy is defined as an increment in CD4 cell count that averages 100–150 cells/mm per year with an accelerated response in the first 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. However, some patients may experience a slower increase of CD4+ T cell counts particularly when anti-retroviral therapy (ART) were initiated at very low baseline CD4 count levels.[1]

CD4 counts should be monitored 4-6 months after initiation of ARV to:

a. assess immunologic response to antiretroviral therapy
b. assess the need to discontinue prophylaxis for opportunistic infections

Once the HIV viral load is suppressed, less frequent monitoring of CD4 cell count (i.e. every 6 months to 1 year) is reasonable

HIV Viral Load

HIV viral load is more accurate and reliable than CD4+ T-cell count to monitor treatment response and for early detection of treatment failure. [5]

HIV Viral Load is Recommended :

a. just before initiation of ART**
b. every 4 to 6 months after initiation of ART to assess treatment response and for early detection of treatment failure
c. every 6 to 12 months in patients who have achieved virological suppression for ≥ 1 year.
d. before changing treatment regimes.

**subjected to resource availability as HIV viral load is an expensive test

Effective therapy should generally result in a 10-fold (1.0 log10) 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 and drug interactions (see also "Initial assessment of treatment failure" in chapter 4).

Monitoring other parameters (Refer Table 4)

The frequency of monitoring depends on the response to ART and the choice of drugs. At the minimum 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.

Co-Trimoxazole Preventive 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.[6]

Table 5 • PCP Prophylaxis

When To Start	What To Start	When To Stop
i. CD4 count of <200/µL or CD4 percentage of <14% ii. Oropharyngeal candidiasis iii. Opportunistic infections / AIDS defining illness iv. Patient who has completed successful treatment for PCP	Co-trimoxazole One double-strength (DS) tablet or two single-strength (SS) tablets once daily Total daily dose is 960 mg (800 mg sulfamethoxazole plus 160 mg trimethoprim)	When CD4 > 200 for two consecutive readings or when CD4 100-200 cells/µL AND HIV-VL is undetectable more than once

Co-Trimoxazole in Pregnant / Lactating Women

Women who fulfil the criteria for co-trimoxazole prophylaxis should continue it throughout their pregnancy. If a woman requires co-trimoxazole prophylaxis during pregnancy, it should be started regardless of the stage of pregnancy.

Contraidications to Co-Trimoxazole Preventive Therapy

Severe allergy to sulfa drugs, severe liver disease, severe anemia or severe pancytopenia. As an alternative, Dapsone at a dose of 100 mg daily may be used.[8]

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 6 • Protocol for Co-Trimoxazole Desensitization[7]

Step	Dose
Day 1	80mg SMX + 16mgTMP (2ml oral suspension)
Day 2	160mg SMX + 32mgTMP (4ml oral suspension)
Day 3	240mg SMX + 48mgTMP (6ml oral suspension)
Day 4	320mg SMX + 64mgTMP (8ml oral suspension)
Day 5	1 SS Co-trimoxazole tablet
Day 6	2 SS Co-trimoxazole tablet

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

Pre ART Counseling

Patients should be given the opportunity to be involved in making decisions about their treatment. The most important time to address the need for treatment adherence is before starting therapy.

People starting treatment should understand that the first line ART offers the best opportunity for effective viral suppression and immune recovery, and that successful ART requires them to take the medications exactly as prescribed.

Pre-HAART counseling

- To provide general knowledge of HIV and ARV medications
- To explain benefits of ARVs
- To explain & clarify potential adverse effects and offer possible solutions
- To discuss the timing for ARV initiation
- To elucidate the rules for treatment success, especially the importance of commitment and medication adherence
- To assess willingness and readiness to initiate ARV
- To explain the ARV regimen, dosage and scheduling
- To explore patient's concerns with possible adverse social consequences (such as disclosure or interference with lifestyle) and socio-economic factors (poverty, housing) that could impact adherence
- To provide solutions to overcome patient's perceived barriers to adherence
- To discuss follow-up and monitoring visits. Pre-HAART pill training may be required to ensure medication compliance (case to case basis)

HAART counseling

- To educate patient about the expected clinical, immunological and virological response
- To ensure that patient knows the correct dosage and management of potential adverse effects
- To develop an individualized medication schedule (link to patient's daily social activities and lifestyle)
- To plan follow up sessions and provide contact details if urgent consultation is required due to adverse effects
- To discuss the possible occurence of IRIS after starting HAART

Adherence to ART

ART adherence is the key to successful HIV treatment

For ART, a high level of sustained adherence is necessary to (a) suppress viral replication and improve immunological and clinical outcomes (b) decrease the risk of developing ARV drug resistance and (c) reduce the risk of transmitting HIV.

Adherence remains a challenge despite simplified regimes and minimum pill burden. There is no gold standard for the assessment of adherence. Although patient self-report of adherence predictably overestimates adherence by as much as 20%,[3]this method is still associated with virological responses.

A patient's report of suboptimal adherence is a strong indicator of non adherence and should be taken seriously. A survey of all doses missed during the past 3 days or the past week accurately reflects longitudinal adherence and is the most practical and readily available tool for adherence assessments in clinical trials and in clinical practice.

Interventions to Improve Adherence

Before writing the first prescription, the clinician should assess the patient's readiness to take medications, including information on factors that may limit adherence (psychiatric illness, active drug use, etc.) making additional support necessary; the patient's understanding of the disease and the regimen; and the patient's social support, housing arrangements, work and home situation, and daily schedules.

Prescribing regimens that are simple to take, have a low pill burden and low-frequency dosing, have no food restrictions, and have low incidence and severity of adverse effects will facilitate adherence.

Patients should understand that their first regimen usually offers the best chance of long-term treatment success and the prevention of drug resistance. Given that ART efficacy is dependent on good adherence, clinicians should identify barriers to adherence such as a patient's schedule, competing psychosocial needs and literacy level before treatment is initiated.

Assessment of adherence is crucial at every clinic visit.

Table 7 • Strategies to Improve Adherence to Antiretroviral Therapy

Strategies	Examples
Multidisciplinary team approach	Provide an accessible, trusting relationship between the nurse counselors, family members, social workers, peer support group and pharmacists
Establish patients' readiness to start ART	
Assess and simplify the regimen	
Identify barriers to adherence	• Psychosocial issues • Active substance abuse or high risk of relapse • Low literacy • Busy daily schedule and/or travel away from home • Nondisclosure of HIV diagnosis • Skepticism about ART • Lack of continuous access to medications
Provide resources for the patient	• Referrals for mental health and/or substance abuse treatment • Continuous pill supply- e.g. SPUB, Postage of medication, drive through counters, prepackaged medications • Pillboxes
Assess adherence at every clinic visit	**Use a simple checklist that the patient can complete in the waiting room** • Ensure that other members of the health care team also assess adherence • Ask the patient open-ended questions (e.g., *In the last 3 days, please tell me how you took your medicines.*)
Identify the type of nonadherence • Failure to fill the prescription(s) • Failure to take the right dose(s) at the right time(s) **Identify reasons for nonadherence** • Adverse effects from medications • Complexity of regimen (pill burden, dosing frequency, etc.) • Difficulty swallowing large pills • Forgetfulness • Failure to understand dosing instructions • Inadequate understanding of drug resistance and its relationship to adherence • Pill fatigue • Other potential barriers	

Increase Retention and Linkage to Care

'Retention in HIV care' is defined as continuous engagement from the time of diagnosis. It begins from the moment of initial engagement in care, when a person with HIV is linked successfully to services, to assessment for eligibility and subsequent initiation of ART and retention in lifelong care. Retention is critical in reducing HIV-related morbidity and mortality, reducing the incidence of new infections, and development of ART resistance.

Table 8 • Factors Affecting Retention in the Health System

Factors Related to the Health System	Interventions
Multiple clinic visits and long waiting time.	• Point of care testing where feasible to reduce frequency of clinic visits
HIV services situated too far away from patient	• Decentralizing HIV services to district hospitals and health Clinics with Family Medicine Specialist. • Scheduled facility visits • Reduce waiting time at the facility: 1. Appointment system 2. Same day clinical consultation, blood taking & collection of medicines • Link, integrate and coordinate care with various services available in the same facility e.g. HIV care, tuberculosis clinic, methadone clinic, sexually transmitted infection clinic (STI) etc.
Supply of ARV drugs complex ARV	• Optimizing pharmaceutical supply management systems e.g. "Sistem pendispensan ubat bersepadu" (SPUB), delivery of ARV drugs by postage and flexible collection time such ie during weekends and after office hours.
Lack of a system for monitoring retention in care	• Implement systems for patient monitoring across the continuum of care, including cohort analysis and patient tracking systems
Lack of a system for transferring people across different points of care	• Interlinked patient monitoring system across services for HIV, TB, maternal and child health and PMTCT; system for transitioning from paediatric/adolescent to adult services and from maternal and child health and TB services to chronic HIV care • Transfer of care for patients upon release from prison and ensure smooth transfer between prisons
Lack of accurate information for patients and their family or peer support groups	• Engage and integrate community health workers, volunteers and people living with HIV in peer support, patient education and counseling, and community-level support
Poor relationship between patient and care provider	• Train health workers on how to: reduce stigma; improve treatment preparedness, adherence and retention; provide adherence support and care for key populations; and provide simplified approaches for educating patients and their families.

Factors Related to the People Receiving HIV Care	Interventions
	• (Attachment of nurses from primary care center to Infectious Disease Clinic in tertiary hospitals to learn management of HIV patients; encourage qualified nurses to pursue post basic HIV counselor training)
Forgetfulness, life stress, stigma and discrimination	• Peer and family support • Link to community support group
Co morbidities, substance and alcohol use and mental health disorders	• Link HIV positive patients with mental health disorders, alcohol and other substance use to psychiatric services, peer support groups, methadone clinics and Agensi Antidadah Kebangsaan (AADK).
Patient knowledge and belief related to HIV infection, its course and treatment	• Integrate the education of patients and their families, broaden community literacy via education and community engagement

LINKAGE TO CARE

Linkage to care is assisting people with HIV to enter medical care. Linkage to care involves: educating patients about the health and prevention benefits of being in care, establishing infrastructures to link people to care.

Integrating and linking services will reduce missed opportunities for initiating ARV drugs, enhance long-term adherence support and optimize patient retention in care.

Linkage to Care • Step 1 Discussing the Test Result with the Patient

Doctors need to confirm a positive result following a rapid HIV test. All positive HIV screening test must have a confirmatory test e.g. Western Blot or line immunoassay especially in asymptomatic patient and those who deny high risk behavior or exposure.

Linkage to Care • Step 2 Basic Counseling About the Disease and Determining Social Concerns

Basic information about the disease, mode of transmission and the need to reduce risk behavior must be informed to patients. Provide the patient with written pamphlets available in the clinic. Address the individual needs and concerns, including sources of emotional support, follow up plan and disclosure of status to partners.

Emphasize that test results are confidential, but the case will be notified to the Ministry of Health and the patient will be contacted by the health inspector. Inform patients that sexual partners and/or needle sharing partners need to be contacted and the health inspector can help them notify partners.

Educate patients on the importance of ongoing, regular health care for their HIV infection even though they may feel healthy at the time of diagnosis.

Linkage to Care • Step 3 Identify Clinics or Hospitals Nearest to Patient Which Provide HIV Services

Put in place convenient appointment arrangements with referral clinicians / counselor nurse to minimize waiting times for appointments. Also confirm the process of referral including referral letters and basic blood investigations required prior to review. Extra effort such as provision of transportation and additional appointment reminders will promote regular clinic visits.

Linkage to Care • Step 4 Track Referrals

Track referrals and put in place a strategy for when patients fail to turn up at the clinics. After a predetermined period, if the doctor doesn't hear from the referred specialist, the tracking system would remind the referring doctor to check if the patient followed through with the appointment.

Linkage to Care • Step 5 Referral to Peer Support Group / Non Governmental Organizations (NGOs) Where Available

These trained peers or NGOs work to build trusting relationships with patients and help them improve their understanding of how to successfully access services.

Linkage to care also involve integrating and linking patients to related services such as genitourinary / sexual health clinic for sexually transmitted infections, maternal and child health for pregnant ladies diagnosed with HIV or a child born to a HIV positive mother, referral to chest clinic for Tuberculosis co-infection and methadone clinic for drug dependence, shelter homes for those with poor social support.

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Table 9 • When to Start ART[1]

Population	Recommendation
Adults and dolescents (>10 years)	Initiate ART if CD4 cell count < 350 cells/mm^3
	For patients who have a CD4 count > 350 but < 500 cells/mm^3 ART may be considered for those who are 1. In a serodiscordant relationship [refer to Chapter 13] 2. Highly motivated to comply with treatment 3. Pregnant or breastfeeding [refer to Chapter 7] 4. Coinfected with Hep B [refer to Chapter 11] 5. MSM who cannot adhere to barrier methods 6. Active TB disease [refer to Chapter 10]

Primary HIV Infection

There is inadequate data on the clinical benefit of antiretroviral therapy in primary HIV Infection (PHI)

When to Start ART After an 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. Drug–drug interactions, additive adverse effects, high pill burden, patient adherence and paradoxical reactions may also pose problems. 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. [2]

In patients with severe or extensive OIs, ART 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 for emergence or reactivation of OIs and/or IRIS must be undertaken. 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.

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How to Choose 1st line ART

Agents used in the first line regime should be safe, effective and tolerable.
2NRTI +1 NNRTI is the preferred option.

Adult	**Preferred First Line** TDF + FTC + EFV	**Alternative** AZT+ 3TC + EFV (or NVP) ABC + 3TC + EFV (or NVP) TDF + FTC + NVP
	• TDF/FTC + Raltegravir (if intolerant of nNRTI)	**PI-Based Regimens:** • ATV/r plus TDF/FTC • LPV/r plus TDF/FTCa
Pregnant	Refer PMTCT section	

Patients who cannot tolerate or develop adverse reactions to the above agents should be referred to the ID physician.

Choice of Nucleoside Reverse Transcriptase Inhibitors (NRTI)
TDF and AZT generally are comparable in terms of efficacy[1] however some studies have shown better efficacy and less side effects with Tenofovir based therapy compared to Zidovudine.[2,3,4] The use of stavudine (d4T) is discouraged. For pts who are started on d4T, it should be switched to TDF or AZT after the first 6 months to avoid its long term adverse events.[5]

In special circumstances where the preferred regimens are not suitable because of toxicities or anticipated drug-drug interactions, regimens containing Abacavir (ABC) may be considered in cases where HIV viral load is < 100,000 copies/ml.

Initiating Nevirapine:
Lead-in NVP dosing 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. The lead-in dose 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 regime 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 significant 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.

Stopping / Interrupting NNRTI

NNRTIs have low genetic barrier to resistance with long half lives. Risk of resistance is high with treatment interruptions. Abrupt discontinuation of a regimen containing NNRTI can lead to periods of NNRTI "monotherapy'" with risk of NNRTI resistance.

Stopping either Nevirapine (NVP) or Efavirenz (EFV)

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

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Management of Treatment Failure: After First Line Treatment

Definition of Treatment Failure

The aim of antiretroviral therapy is to achieve durable HIV virologic suppression, which leads to good treatment outcomes. Conversely, antiretroviral treatment failure can be defined as a suboptimal response to therapy leading to loss of virologic control. This is most accurately recognized by measuring and detecting a significantly raised HIV viral load (plasma HIV-1 RNA levels) while the patient is on highly active antiretroviral therapy.

Successful Virologic Suppression

Defined as having a sustained viral load that is undetectable (e.g. viral load <40 copies/ml where 40 is the lower limit of viral load detection)

Viral "blips"

Defined as isolated transient rises in viral load to above detectable level while on treatment after having achieved prior viral suppression and is followed by re-suppression. The levels generally do not exceed 200 copies/ml.

It may reflect technical variations in laboratory assay performance, or biological events associated with viral replication (immunization, other viral infection).

Isolated "blips" are 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 below – low level viremia)

Low Level Viremia

Defined as a repeatedly detectable viral load that is < 1000 copies/ml. This group comprise a spectrum of patients at different strata of viral loads. It is recognized that those with a higher level of detectable viremia have a higher tendency to develop virologic resistance and subsequent failure. Patients in this group would benefit from attention given to strict adherence to the current regime and close monitoring for subsequent virologic failure.

Virologic Failure

WHO defines virologic failure as either an incomplete virologic response which is a failure to achieve HIV viral load <1000 copies/ml 4–6 months after starting therapy or a virologic rebound where after previous virologic suppression, there is a persistent HIV viral load to > 1000 copies/ml while on the same regime.

Assessing for treatment failure through other means like a drop in CD4 or on a clinical basis would lead to delays in diagnosis of failure and this predisposes to the selection of more drug resistance mutations, especially in the NRTI component.

Initial Assessment of Treatment Failure

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

Factors that increase the risk of treatment failure include:

- Previous ARV history using less potent regimens
- higher baseline HIV RNA level
- lower pre-treatment or nadir CD4 T-cell count
- prior AIDS diagnosis
- co morbidities (e.g., depression, active substance use)
- presence of drug-resistant virus at baseline
- prior treatment failure, with development of drug resistance or cross resistance
- incomplete medication adherence and missed clinic appointments
- drug side effects and toxicity
- suboptimal pharmacokinetics (variable absorption, metabolism, food/fasting requirements, adverse drug-drug interactions with concomitant medications)

Some factors have not been associated with treatment failure and these include gender, pregnancy, and history of past substance use.

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 non-adherence (e.g. poor 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:
Ideally, obtain resistance testing (where available) while the patient is on the failing regimen or if not possible, within 4 weeks after discontinuation

II. Physical Examination to Assess for Signs of Clinical Progression.

- **Low level viremia (viral load <1,000 copies/mL).**
  There is no consensus on managing patients with viral load above detection but <200 copies/mL. The patient's adherence must be assessed and optimized. Patients with "blips" do not require changes in treatment. Viral loads persistently >200 copies/mL but < 1000 copies/mL should be considered as possible virologic failure. Viral load levels should be repeated once adherence has been addressed.

- **Viral load persistently >1,000 copies/mL and no drug resistance identified on resistance testing.**
  Assess and address adherence as this is the most likely cause of virologic failure. Sometimes drug-drug interactions may also lead to inadequate plasma levels leading to failure to suppress the viral load.

- **Viral load persistently >1,000 copies/mL and drug resistance identified on resistance testing.**
  Consider changing to second line regime as soon as adherence can be ascertained. This is to minimize the risk of accumulated viral resistance. The new regimen should include at least two, and preferably three, fully active agents.

- **Viral load persistently >1,000 copies/mL and no resistance testing available.**
  Closely assess if the patient has been adherent for the last 4-6 months prior to the recent viral load test. Collaborate this history with next of kin if possible or relevant. If adherence is very likely, consider this as treatment failure due to resistance.

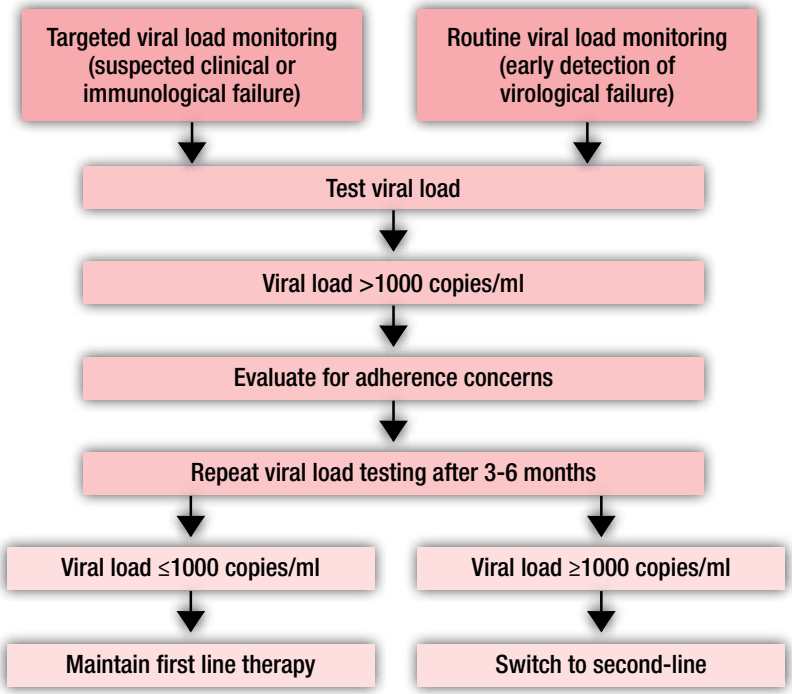
General Principles of Changing Therapy

a. 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.
b. Ideally the new regimen should consists of at least 2, and preferably 3 fully active agents from at least one new class[5]
c. In general, adding a single, fully active antiretroviral drug to a regimen is not recommended because of the risk of development of rapid resistance to that single drug.

When to Switch

There is limited long term clinical data to guide us on the optimal time to switch therapy. Our recommended approach allows detectable viremia up to a level of 1,000 copies/mL, in keeping with WHO recommendations before considering switching. Below is an algorithm from the WHO guidelines on when to switch.

Viral Load Testing Strategies to Detect or Confirm Treatment Failure and Switching ART Regimen in Adults, Adolescents and Children



Adapted from WHO Consolidated ARV guidelines 2013

The decision to switch should also be guided by the availability of second line treatment options which are likely to suppress viral load to undetectable levels and which the patient is able to tolerate.

Choice of Second Line Regimes for Treatment Failures

When the current first line regimes based on NNRTI and 2 NRTI (usually lamivudine with AZT, d4T or TDF) fails, predicted resistance will be towards lamivudine (M184V/I) and NNRTIs (Y181C/I/V,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 10 • Recommended second line regime[1]

Failing First Line ART Regime	Recommended Second Line ART Regime		
	NRTI *	PI	Integrase Inhibitors
AZT/D4T+3TC +NNRT	**Preferred:** TDF+3TC/FTC **Alternatives:** ABC+3TC	**Boosted PI–either** Lopinavir+Ritonovir Atazanavir+Ritonovir Darunavir+Ritonavir	
TDF**+3TC/FTC +NNRTI	AZT +3TC		
TDF /AZT / d4T +3TC/FTC+NNRTI		Lopinavir+Ritonovir***	Raltegravir***

Other second line drugs to replace NRTI backbone

* ABC may be used as potential back-up options in special circumstances (eg concommittant renal failure that precludes use of TDF or a past history of anaemia precluding use of AZT).
3TC should be continued in second line regimes even though there is a strong likelihood of 3TC resistant mutations when the 1st line regimes fail. This is because the continued presence of the 3TC resistant mutation (M184V/I) confers a fitness toll on the HIV virus.

** TDF should not be discontinued in the second line regime in patients with underlying Hepatitis B as this can lead to flares in hepatitis.

*** Kaletra and Raltegravir combination has been proven in one randomized trial to be as efficacious as standard second line regime consisting of 2 optimized NRTIs + 1 PI/r
Etravirine is a second generation NNRTI which has limited cross class-resistance and would be an option as a replacement for the NNRTI component of the regime. However this drug should only be considered in early treatment failure and would require prior HIV resistant testing while on the failing first line therapy.
Raltegravir is an integrase inhibitor that may be considered as a PI substitute if there is no PI option and HIV resistant testing affords a strong NRTI back bone. It has a lower genetic barrier to resistance and is not as efficacious as PIs.

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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. Viral load of up to 20 000 copies/ml may be acceptable in this group of patients.

In a patient with no other HAART option, the decision whether to continue the failing regime or not will be based on cost and side effect of the drugs in the failing regime. If the patient is currently on therapy, continuing the failing regime rather then stopping it has been shown to be beneficial provided that the patient has not developed any side effects to the drugs and is clinically well. 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.

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/I mutation).[3]

Viral Resistance Testing

Genotypic assays detect drug resistance mutations present in relevant viral genes. This test is not widely available at this time. If available, they should be performed in the following circumstances:

- Prior to any change in antiretroviral therapy secondary to virologic failure. This is especially important when planning for salvage regimes in second line ART failure involving protease inhibitors as the drug resistance pattern for these drugs are less predictable.
- Prior to a change in regime for patients who are receiving a suboptimal regime including monotherapy or dual therapy. This includes mothers who may be receiving limited ART for the sole purpose of preventing vertical transmission.

In order to optimize the accuracy of the results, testing should only be done when the viral load is > 1000 copies/ml and with the patient being currently adherent to the regime. Ideally, resistance testing is performed while the patient is on the failing regimen or if not possible, within 4 weeks after discontinuation.

When interpreting a drug resistance test, the presence of a fully sensitive virus in a patient who is currently failing HAART would suggest probable non adherence to therapy. The absence of a particular resistance does not rule out the possibility of underlying drug resistance. This may occur because the patient is currently not on that particular drug or due to a low frequency of certain viral variants not picked up by the test. Whenever in doubt, the interpretation of a resistance test should be discussed with an ID Physician.

Detected drug resistance is cumulative for a given individual; thus, all prior treatment history and resistance test results should be taken into account.

Introduction

Antenatal combination antiretroviral therapy (cART) is now the recommended method for prevention of maternal-to-child transmission (PMTCT). cART must be started in all pregnant mothers who are HIV+ regardless of CD4 count.

Ideally cART should be started at 14 weeks of pregnancy. cART is still efficacious when started as late as 28 weeks of pregnancy. The treatment of women who start cART after week 28 must be discussed with an ID physician. Strict adherence to cART must be stressed throughout the pregnancy.

A viral load must be done between weeks 32-36 to determine ongoing risk of transmission to the fetus. The mode of delivery will also be determined by the result.

Women with CD4 < 350
This group of women must be started on cART as soon as possible. cART can be started even in the first trimester in women presenting with OIs or WHO clinical stages 3 and 4. cART will be continued for life after delivery.

Women with CD4 > 350
These patients will also need cART for PMTCT. In this scenario commencement of cART may be delayed until week 14 of pregnancy. Continuation of cART post-delivery (Option B +) is recommended for patients with CD4 > 350 who are:

1. Motivated
2. In a serodiscordant sexual relationship
3. Unable to adhere to contraceptive methods
4. Co-infected with Hep B
5. Insist on breastfeeding

The decision to continue (Option B +) or stop cART post-delivery (Option B) must be discussed with the patient.

Women Who are Stable on cART Before Pregnancy
In general the existing cART is to be continued throughout pregnancy and after delivery. Special effort must be made to determine the current CD4 and Viral load during the early stages of pregnancy. Should the patient be experiencing virological failure on her current regime, consultation with an ID physician is strongly recommended.

Intrapartum Management of Women Receiving cART During Pregnancy
In the past IV ZDV was recommended routinely for all women during the intrapartum period regardless of viral load. However current evidence suggests that intrapartum IV ZDV has no additional benefit in prevention of vertical transmission in pregnant women on cART with suppressed viral load.

Women Who Present in Labour With No Prior ARV Exposure

For the woman who is diagnosed with HIV infection in labor who has not received prior ARVs, start IV ZDV infusion (2mg/kg for the 1st hour followed by 1mg/kg/h subsequently) immediately. Single dose NVP for the mother is not necessary. Giving intrapartum Nevirapine to the mother may select for resistance to NNRTIs and limit future ARV options.[2,3]

The Pediatrician caring for the newborn must be notified to ensure appropriate post exposure ARV prophylaxis for the infant.[4,5] The HIV exposed infant should receive 6 weeks of oral zidovudine and 3 doses of nevirapine at birth, 48 hours later and 96 hours after the 2nd dose.

Choice of Agents Used for PMTCT

cART used during pregnancy must consist of 2 RTIs plus either a NNRTI or a boosted PI. The choice of agents is listed in Table 1.

Preferred	Alternative
TDF + 3TC (or FTC) + EFV*	AZT + 3TC + EFV AZT + 3TC + NVP# TDF + 3TC (or FTC) + NVP# TDF + 3TC (or FTC) + LPV/RTV

* In the past Efavirenz was considered a Category D drug and contraindicated in the first trimester of pregnancy. However there is now good level safety evidence to recommend it as the preferred NNRTI even in the first trimester.[6]

Nevirapine must be used with caution in women with CD4 > 3507.

Mode of Delivery

Pre-labor Elective Caesarean Section (PLCS) has been proven to further reduce the risk of transmission.[8,9] The decision between performing PLCS or allowing spontaneous vaginal delivery (SVD) is based largely on the VL at 32-36 weeks of gestation and whether the mother has received any ARVs in the antenatal period.

Women who have received cART before pregnancy or antenatally and have achieved maximal VL suppression, have a choice between PLCS or SVD. There is no additional advantage of PLCS over SVD in terms of reduction of transmission[10] in this group.

Viral load at 32-36 weeks	Mode of delivery
< 50 copies/m	SVD
50-399 copies/ml	PLCS recommended *
> 400 copies/ml or unknown viral load	PLCS

* Take into account the trajectory of the viral load leading up to time of delivery, length of time on ARVs, adherence issues, obstetric factors and the woman's views.

Women who are diagnosed with HIV infection during labor or following rupture of membrane (ROM) should be managed on a case by case basis. There is insufficient data to routinely recommend caesarean section in this scenario. The decision for the mode of delivery has to take into account the duration of ROM and the expected time of delivery. After ROM there is an increased risk of transmission of 2% per hour.

For women with viral load < 50, who present after ROM, Caesarean section is not recommended.[11] However for those with VL > 50 or who have unknown VL, CS is recommended within 4 hours of ROM.

Breast-Feeding

Breast-feeding is not recommended as it is associated with risk of transmission upto 14%.[5] For women on cART compliance must be stressed.

Notes

Option B + Lifelong cART for all pregnant women (regardless of CD4)	Start cART and maintain post-delivery
Option B cART only during pregnancy for women with CD4 > 350	Start cART and stop post-delivery

To avoid resistance mutation please refer to Chapter 5 for ways to cease NNRTI based regimes.

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Adverse events (AEs) occur with all antiretroviral agents and is a major reason for switching or discontinuation of therapy and poor 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. [See Annex 5 Severity Grading]
3. If the reaction is mild or moderate, do not discontinue ART (except for NVP-induced rash / hepatotoxicity). 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 profile. [See 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 a known case of virological failure.
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'

See Annex 4 • Adverse Events of Antiretroviral Drugs for a complete list of the adverse events of ARVs

Table 11 • Individual NRTI Drug Substitutions For Toxicity and Intolerance

ARV Drug	Major Toxicities	Risk Factors	Suggested Management
ABC	Hypersensitivity reaction	Presence of HLA-B*5701 gene (test available in select labs only)	Substitute with TDF / ZDV
d4T	Lactic acidosis, acute pancreatitis, Hepatic steatosis	BMI > 25 (or body weight > 75kg) Long-term exposure to thymidine analogues	Substitute with TDF / ABC
	Lipodystrophy Peripheral neuropathy (esp. ascending neuromuscular weakness)	Older age CD4 count ≤200 cells / mm^3 Concomitant use OF isoniazid or didanosine	
ddI	Acute pancreatitis, lactic acidosis Hepatic steatosis	BMI > 25 (or body weight > 75kg) Long-term exposure to thymidine analogues	Substitute with TDF / ABC
	Peripheral neuropathy	Older age CD4 count ≤ 200 cells / mm^3 Concomitant use of isoniazid or d4T	
TDF	Renal tubular toxicity, Fanconi syndrome	Underlying kidney disease Older age BMI < 18.5 (or body weight > 50kg) Underlying diabetes mellitus, uncontrolled hypertension Concomitant use of nephrotoxic drugs or a boosted PI	Substitute with ZDV / ABC
	Decrease in bone mineral density	History of osteomalacia and fracture At risk of osteoporosis / bone loss	
	Hepatic flares	When TDF withdrawn or HBV resistance develops	Use alternative drug for Hep. B treatment (ie. entecavir)
ZDV	Anaemia, neutropaenia[1] Myopathy Lipodystrophy (rare)	Baseline anaemia / neutropaenia CD4 count ≤ 200 cells /mm^3	Substitute with TDF / ABC
EFV	Hallucinations, psychosis Depression Suicidal ideation Persistent insomnia	History of psychiatric illness Concomitant use of substance with neuropsychiatric effects Genetic factors resulting in high serum EFV concentration Increased absorption with food.	Substitute with NVP
NVP	Hepatitis (with / without fever) Severe skin rash (SJS)	Females with baseline CD4 > 250 cells / mm^3 Males with baseline CD4 > 400 cells / mm^3	Substitute with EFV / PI-based regime

Table 12 • Adverse Events of Antiretroviral Drugs

Bone Marrow Suppression		
Associated ARV	**Comments**	**Management**
Zidovudine (ZDV)	Incidence: (anemia) adult 1%, pediatric 23%; (leukopenia) 39% • Avoid concurrent bone marrow suppressants • Monitor FBC with differential at weeks–4, 8, 12 (more frequently in patients at risk)	Discontinue ZDV if Hb has dropped ≥ 25% of baseline / <8.0 g/dL OR when patient develops symptomatic anemia and / or leukopenia
Central Nervous System Effects		
Associated ARV	**Comments**	**Management**
Efavirenz (EFV)	Incidence: 40%; only 3% severe enough to justify discontinuation of EFV. Symptoms include: • Vivid / abnormal 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 Insomnia, mood fluctuations, depression, depersonalization, paranoid delusions, confusion and even suicidal ideation may occur. Potential additive effect with alcohol and other psychoactive drugs. False positive cannabinoid and benzodiazepine urine test	• Symptoms improve with continued EFV. Rarely persists beyond 2-4 weeks. • Take at bedtime or 2–3 hours before bedtime. Avoid heavy / oily food to reduce symptoms. • Avoid driving / operating machinery or other potentially dangerous activities. • If side-effects are severe / life-threatening, to discontinue EFV and tail off NRTIs for 2 weeks, if not for restarting of ARV drugs yet.
Gastrointestinal Intolerance		
Associated ARVs	**Comments**	**Management**
All ARVs, Especially : Protease inhibitors (PIs) Zidovudine (ZDV) Efavirenz (EFV) Tenofovir (TDF)	Symptoms include: abdominal discomfort, loss of appetite, nausea, vomiting, heartburn, abdominal pain, constipation. • Nausea is common with ddI, ZDV (vomiting, 6-25%), more than other NRTIs. Occurs in 2-12% of EFV usage. • Diarrhoea is frequently seen with ZDV (17%), TDF (16%), ddI and all PIs - LPV/r (39-60%)> DRV/r, ATV/r. • Side effects usually resolve after 4-6 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. <u>Nausea and vomiting</u>: • Antiemetic prior to dosing • Switch to less emetogenic ARV if persistent vomiting

Didanosine (ddI)		Diarrhea: • Antimotility agents (e.g., loperamide, diphenoxylate/ atropine) • Monitor pancreatic enzymes Severe GI symptoms: Rehydration and electrolyte replacement as indicated 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. Dose escalation reduces risk of hepatic AE due to hypersensitivity. Higher risk of NVP-associated hepatic AE in ARV-naïve females with baseline CD4 >250 cells/uL and males with baseline CD4 >400 cells/uL. Contraindicated in moderate to severe hepatic impairment (Child-Pugh B or C) NRTI Usually occurs after more than 6 months of therapy - ZDV, d4T (grade 3 / 4: 2-16%), ddI Risk of hepatotoxicity associated with lactic acidosis with microvesicular or macrovesicular hepatic steatosis because of mitochondrial toxicity. PI Usually occurs after weeks to months of treatment Indirect hyperbilirubinemia may occur with IDV (14%) & ATV (35-49%) usage	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)

Hyperlipidemia		
Associated ARV	**Comments**	**Management**
All PIs (except unboosted ATV); EFV > NVP d4T	NNRTIs • EFV is associated with ↑ TG, HDL, LDL (TC ↑ by 20-40%). • Increase in TG, TC and LDL less than with PIs NRTIs • d4T > ZDV > ABC - TG and LDL ↑ PIs • Cause ↑ in LDL, HDL and TG – all RTV-boosted PIs. • TG ↑: LPV/r (3-36%) > DRV/r, ATV/r • Usually seen within 2-3 months of starting PI.	• Lifestyle modifications (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 Table 17 & 18: Drug Interactions for interactions between ARV and lipid-lowering agents*
Hypersensitivity Reaction (HSR)		
Associated ARV	**Comments**	**Management**
Abacavir (ABC)	Incidence: Up to 8% Median onset is 9 days; approximately 90% of reactions occur within the first 6 weeks Symptoms include: • (In descending frequency): fever, skin rash, malaise, nausea, headache, myalgia, chills, diarrhea, vomiting, abdominal pain, dyspnea, arthralgia, and respiratory symptoms. • With continuation of ABC, symptoms may worsen to include hypotension, respiratory distress.	• 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 More severe cases: • Manage with symptomatic support (antipyretic, fluid resuscitation, pressure support if necessary) • Do not rechallenge patients with ABC after suspected HSR, even in patients who are tested (-) for HLA-B*5701.
Gastrointestinal Intolerance		
Protease inhibitors (PIs): IDV/r, LPV/r NRTIs: ZDV, d4T, ddI	It occurs weeks to months after beginning 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 ARV	**Comments**	**Management**

d4T > ddI > ZDV > 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 include:
	• Nonspecific 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)
	  • 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 Lipodystrophy
		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 > 5mmol/L or lactic acidosis:
		
		• Stop ARVs
		• Exclude other precipitating factors
		• Intensive care support
		• To consider: IV thiamine and/or riboflavin / bicarbonate infusions / haemodialysis
		
		<u>ARV treatment options</u>:
		
		Use NRTIs with less propensity for mitochondrial toxicity (ABC, TDF)
		
		Recommend close monitoring of serum lactate after restarting NRTIs
		
		Consider NRTI-sparing regimen if severe / recurrent lactic acidosis

Lipodystrophy		
Associated ARVs	**Comments**	**Management**
Associated ARVs d4T> ZDV> other NRTIs	Fat wasting (lipoatrophy): face, arms, leg, buttocks – more likely when NRTIs combined with EFV than with RTV-boosted PI Fat accumulation: Abdomen, neck, gynaecomastia, buffalo hump, multiple lipomas, Cushingoid appearance without Cushing's disease. Trunk fat ↑ was noted with EFV, PI and RAL-containing regimes, but no causal link has yet been established.	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: <u>Lipoatrophy</u>: Facial filling with collagen, synthetic polymers or silicone <u>Lipodystrophy</u>: Liposuction

Nephrotoxicity / Urolithiasis		
Associated ARV	**Comments**	**Management**
Tenofovir (TDF) Atazanavir (ATV)	DF Symptoms include: ↑ serum creatinine, proteinuria, hypophosphatemia, urinary phosphate wasting, glycosuria, hypokalemia, nonanion gap metabolic acidosis Concurrent use with PI: ↑ risk ATV May cause kidney stone / crystal formation	Prevention Drink at least 1.5 - 2 liters of non-caffeinated fluid (preferably water) per day – not sure about TDF Treatment 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 use. 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 deficits; symptoms may be irreversible in some patients *Do not rechallenge patient with offending agent.*
Pancreatitis		
Associated ARVs	**Comments**	**Management**
ddI alone ddI + d4T ddi + TDF	ddI alone: 1%–7% ddI with d4T or TDF : ↑ frequency Do not use ddI in patients with history of pancreatitis ; patients > 65 years old had higher incidence of pancreatitis compared to younger patients. Avoid concomitant use of ddI with d4T or TDF	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 ARV	**Comments**	**Management**
d4T > ddi	It occurs weeks or months after initiating therapy Usually presents with a distal symmetrical distribution and sensorimotor paralysis. *Note:* *HIV-associated polyneuropathy does not worsen and may improve with prolonged ARV treatment.*	Discontinuing 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 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 discontinuation of the offending drug, but may initially increase in intensity ('coasting') and are not always fully reversible.*
Rash		
Associated ARV	**Comments**	**Management**
Nevirapine (NVP)	Rash is greatest in the first 6 weeks of treatment (Malaysian data: >20%). Constitutional symptoms : • Fever> 37 ºC • Blistering • Oral lesions • Conjuctivitis • Significant elevations in LFTs • Facial oedema • Myalgia/arthralgia • Generalized malaise	In the presence of mildto 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 see Stopping / Interrupting NNRTI, P25 If NVP is interrupted for > 7days, reintroduce with 200mg/day lead-in.

Stevens-Johnson Syndrome (SJS) / Toxic Epidermal Necrosis (TEN)		
Associated ARV	**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. If offending drug is NVP, may consider use of EFV. • Aggressive symptomatic support

Table 13 • NRTI and Common Adverse Events

Drug	Adverse Events
Abacavir (ABC)	• Hypersensitivity reaction symptoms
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 hepatitis flare may occur in HBV co-infected patients who discontinue 3TC.
Stavudine (d4T)	• Peripheral neuropathy • Lipoatrophy • Pancratitis • Lactic acidosis with hepatic steatosis (rare but potentially life-threatening toxicity) • Hyperlipidemia • Rapidly progressive ascending neuromuscular weakness (rare)
Tenofovir (TDF)	• Asthenia, headache, diarrhea, nausea, vomiting, and flatulence • Renal insufficiency †, Fanconi syndrome • Osteomalacia • Potential for decrease in bone mineral density • Severe acute hepatitis flare may occur in HBV co-infected patients who discontinue TDF
Zidovudine (ZDV)	• 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 first 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 14 • NNRTI and Common Adverse Events

Drug	Adverse Events
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, but has been evaluated to be safe for 1st trimester use
Nevirapine (NVP)	• Rash, including Stevens-Johnson syndrome • Symptomatic hepatitis, including fatal hepatic necrosis, has been reported

Table 15 • Protease Inhibitors and Common Adverse Events

Drug	Adverse Events
Atazanavir (ATZ)	• Indirect hyperbilirubinemia • Prolonged PR interval—first 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 • Diarrhea, nausea • Headache • Hyperlipidemia • Transaminase elevation • Hyperglycemia • Fat maldistribution • Possible increased bleeding episodes in pts with hemophilia
Lopinavir/Ritonavir (Kaletra-LPV/r)	• GI intolerance, nausea, vomiting, diarrhea • 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, diarrhea • 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 diarrhea • Headache • Elevated transaminase enzymes • Hyperlipidemia • Hyperglycemia • Fat maldistribution • Possible increased bleeding episodes in pts with hemophilia

Table 16 • Integrase Inhibitors and Common Adverse Events

Drug	Adverse Events
Raltegravir (RAL)	• Increased CK; muscle weakness and rhabdomyolysis • Rash (uncommon)

Table 17 • Common PI Drug Interactions and Suggested Management

Key to symbols:
- • These drugs should not be coadministered
- Δ Potential interaction, caution required
- ◊ No clinically significant interaction expected

Concomitant Drug	Protease Inhibitor (PI)	Description of Interaction	Suggested Management
Acid Reducers			
Antacids	Δ ATV/r	↑ pH → ↓ATV solubility; ↓ATV AUC and absorption [3]	Give ATV/r at least 1 hr before or 2 hrs after antacids [3]
H2 Receptor Antagonists	Δ ATV/r	↑pH → ↓ATV solubility; ATV AUC ↓48% when ATV/r was administered 1hr after a single dose of ranitidine 150mg in a study of 12 healthy volunteers[1]	H2-receptor antagonist can be administered with ATV/r but dose should not exceed a dose equivalent to famotidine 40mg BID in treatment naïve patients or 20mg BID in treatment-experienced patients. [4] ATV/r should be administered either simultaneously with or at least 10 hrs after H2-receptor antagonist (which leads to only <20% reduction of ATV AUC) [2,3] *Note:* *PO Famotidine 20mg BID = PO Ranitidine 150mg BID; IV Famotidine 20mg BID = IV Ranitidine 50mg TDS*
	◊ DRV/r, ◊ LPV/r	No significant interaction	
Proton Pump Inhibitors (PPIs)	• ATV/r	AUC of ATV/r ↓~42-76%. [3,5,6] Mechanism is by reduction of ATV solubility due to increased gastric pH.	Co-administration is not recommended. 3 If co-administration is judged unavoidable, PPIs should not exceed dose equivalent of omeprazole 20mg OD and should be administered 12hrs apart from ATV/r.

Concomitant Drug	Protease Inhibitor (PI)	Description of Interaction	Suggested Management
Antifungal			
Fluconazole	◊ All PIs (except tiprinavir)	No significant effect [3,7,8,9,10]	No dose adjustment necessary [3,7,8,9,10]
Itraconazole	Δ ATV/r, Δ DRV/r, Δ LPV/r	Potential for bidirectional inhibition between itraconazole and PIs [3,7,8,9,10]	Do not exceed itraconazole 200mg/day. Use with caution and monitor for toxicities. [3,7,8,9,10]
Ketoconazole	Δ ATV/r, Δ DRV/r, Δ LPV/r	Potential for bidirectional inhibition between itraconazole and PIs [3,7,8,9,10]	Do not exceed ketoconazole 200mg/day. Use with caution and monitor for toxicities. [3,7,8,9,10]
Voriconazole	Δ ATV/r, Δ DRV/r, Δ LPV/r	Low dose RTV 100mg BD decrease voriconazole AUC by 39% [10]	Co-administration of voriconazole and ritonavir-boosted PIs should be avoided, unless an assessment of the benefit/risk to the patient justifies the use of voriconazole.[10]
Antifungal			
Clarithromycin	Δ ATV/r,	Unboosted ATV ↑ clarithromycin AUC 94% and may cause QTc prolongation. No data on RTV-boosted ATV. [3,11]	↓ clarithromycin dose by 50%. Consider alternative therapy. [3]
	Δ DRV/r, Δ LPV/r	Clarithromycin AUC↑57%[12] Clarithromycin AUC↑77%[9] Clarithromycin AUC↑47%[13]	Monitor for clarithromycin-related toxicities. Reduce clarithromycin dose by 50% in CrCl 30-60mL/min; reduce clarithromycin dose by 75% in patient with CrCl < 30mL/min.[7,9]
Erythromycin	Δ DRV/r, Δ LPV/r,	Erythromycin concentrations may increase but no data on the extent of interaction. [7,8,9,10]	Careful monitoring of therapeutic and adverse effects is recommended. [7,8,9,10]
Rifampicin	Δ All PIs	Significant decrease in PI concentrations (up to >80%) [7,8,9,10]	Do not co administer rifampicin and PIs. [7,8,9,10]
Anticonvulsants			
Carbamazepine (CBZ)	Δ ATV/r, Δ LPV/r	Coadministration may increase CBZ levels (up to 46%) and decrease PI concentrations.[3,8,9,14]	Consider alternative anticonvulsant or monitor levels of both drugs and assess virological response. [3,8,9]
	Δ DRV/r	CBZ AUC ↑45%. No significant effect on DRV exposure.[7]	Monitor anticonvulsant level and adjust dose accordingly. [7]
Lamotrigine (LTG)	Δ LPV/r	LTG AUC ↓ 50% due to induction of glucoronidation metabolism. [15] No effect on LPV/r.	Titrate lamotrigine dose to effect. A similar interaction is possible with other RTV-boosted PI.[3,8,10,1]

Concomitant Drug	Protease Inhibitor (PI)	Description of Interaction	Suggested Management
Anticonvulsants			
Phenytoin (PHT) / Phenobarbitone (PHB)	Δ ATV/r, Δ DRV/r, Δ LPV/r	Both PI concentrations and PHT/PHB levels may decrease due to bi-directional interactions. [3,7,8,9,10]	Consider alternative anticonvulsant or monitor levels of both drugs and assess virologic response. Do not co administer with LPV/r once daily. [3,7,8,9,10]
Valproic Acid (VPA)	Δ ATV/r, Δ DRV/r, Δ LPV/r	Possible decrease in VPA level by ritonavir (induces glucoronidation) but no significant effect on PIs. [3,7,8,10,16]	Monitor anticonvulsant level and adjust dose accordingly. [3,7,8,10,16]
Benzodiazepines			
Alprazolam Diazepam	Δ ATV/r, Δ DRV/r, Δ LPV/r	Potential CYP3A4 enzyme inhibition and increase in alprazolam / diazepam concentrations.[17]	Consider starting alprazolam at lower dosage or use alternative benzodiazepine.
Lorazepam	◊ All PIs	No interactions.[18]	Can be safely co-administered.
Midazolam Triazolam	• All PIs	Oral midazolam/triazolam concentrations are significantly increased, hence increasing risk of extreme sedation and respiratory depression. [3,7,8,9,10] (Kaletra increase AUC of oral midazolam by 13-fold and parenteral midazolam by 4-fold)[9]	Do not co administer. Parenteral midazolam can be used with caution as a single dose and can be given in a monitored situation for procedural sedation. [3,7,8,9,10]
Zolpidem	Δ All PIs	Potential CYP3A4 enzyme inhibition by PIs and increase in zolpidem concentrations.[17]	Consider starting zolpidem at lower dosage or use alternative benzodiazepine.
Hormonal Contraceptives			
Hormonal contraceptives	Δ ATV/r	Ethinyl estradiol AUC↓19% [19]	Oral contraceptive should contain at least 35mcg of ethinyl estradiol.[19]
	Δ DRV/r, Δ LPV/r	Ethinyl estradiol AUC↓44-55% [20,21]No clinically significant interactions.[8,9]	Use alternative or additional method [7,9]

Concomitant Drug	Protease Inhibitor (PI)	Description of Interaction	Suggested Management
HMG-CO A Reductase inhibitors			
Atorvastatin	Δ All PIs	Potential increase in atorvastatin concentrations and increased risk of myopathy when co-administered with PIs. [3,7,8,9,10]	Use lowest possible starting dose with careful monitoring for toxicities or consider other HMG-Co A reductase inhibitors with less potential for interaction. [3,7,8,9,10]
Lovastatin Simvastatin	Δ All PIs	Marked increase in lovastatin / simvastatin concentrations may lead to myopathy including rhabdomyolysis. [3,7,8,9,10]	Contraindicated – do not co administer. [3,7,8,9,10]
Pravastatin	Δ DRV/r	Pravastatin AUC ↑81% [22]	Use lowest possible starting dose with careful monitoring [7]
	◊ LPV/r	No clinically significant interactions. [8,9]	No dosage adjustment necessary [8,9]
Antiarrhythmics			
Amiodarone	Δ All PIs	Potential for increased concentrations of amiodarone and risk of life-threatening arrhythmias. [3,7,8,9,10]	Contraindicated – do not co administer. [3,7,8,9,10]
Anticoagulant			
Rivaroxaban	Δ All PIs	Anticoagulant Potential for clinically significant increase in rivaroxaban concentrations which may lead to an increased bleeding risk. [23]	Contraindicated – do not co administer.[23]

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Table 18 • Drug Interactions Between NNRTIs and Other Drugs

Concomitant Drug	NNRTI	Description of Interaction	Suggested Management
Antifungal			
Fluconazole	◊ EFV	No significant effect.[1]	No dosage adjustment necessary.[1]
Itraconazole Ketoconazole	Δ NVP	NVP AUC ↑30-100% [2,3]	Increased risk of hepatotoxicity possible with this combination. Monitor NVP toxicity or use alternative antiretroviral agent.
Voriconazole (VORI)	Δ EFV	Itraconazole AUC ↓39% [1,5] Ketoconazole AUC ↓72% [6]	Dose adjustment for itraconazole may be necessary. Monitor itraconazole level. Avoid combination with ketoconazole.
	Δ NVP	Itraconazole AUC ↓61% [4] Ketoconazole AUC ↓63-72% [7,8] At standard doses (EFV 600mg OD; VORI 200mg BD): [9] VORI AUC ↓80% EFV AUC ↑43%, Cmax ↑37% After dose adjustment of EFV 300mg OD; VORI 300mg BD: [10] VORI AUC ↓55% EFV AUC no change but Cmax ↓14%	Avoid combination and use alternative agent When coadministered, voriconazole maintenance dose must be increased to 400 mg twice daily and efavirenz dose should be reduced by 50% (i.e., to 300 mg once daily). When treatment with voriconazole is stopped, the initial dosage of efavirenz should be restored.
	Δ EFV	After dose adjustment of EFV 300mg OD; VORI 400mg BD: [10] VORI AUC ↓7% EFV AUC ↑17%, Cmax no change	
	Δ NVP	No data available. Potential induction of VORI metabolism by NVP and inhibition of NVP metabolism by VORI. [11]	If co administered, monitor for occurrence of drug toxicity (NVP) and/or lack of efficacy (VORI). [11]
Antimycobacterial			
Clarithromycin	Δ EFV	Clarithromycin AUC ↓39% but 14-OH clarithromycin (active metabolite) AUC ↑34%. EFV AUC ↑11%. [12]	Monitor for efficacy or consider alternative agents such as azithromycin, for MAC treatment.
	Δ NVP	Clarithromycin AUC ↓30% but 14-OH clarithromycin (active metabolite) AUC ↑42-58%. NVP AUC ↑26%. [8,13]	Close monitoring for hepatic abnormalities is recommended.[1,8]

Concomitant Drug	NNRTI	Description of Interaction	Suggested Management
Antimycobacterial			
Rifampicin	Δ EFV	EFV AUC ↓~20% but effect not clinically significant.[1,14,15,16,175]	Maintain EFV 600mg once daily and monitor for virologic response.[1,14,15,16,17]
	Δ NVP	NVP AUC ↓>50%,[8,18,19,20] associated with 2-fold increase in virological failure in patients started on NVP while on rifampicin. There was no difference in virological rebound in patients started on rifampicin-based antiTB regimen while taking nevirapine or efavirenz as compared to patients not on antiTB.[21]	Avoid starting nevirapine in patients with concurrent rifampicin therapy. Consider using rifabutin instead of rifampicin. Monitor efficacy for patients who are stable on nevirapine.[8,20,21]
Anticonvulsants			
Carbamazepine	Δ EFV	CBZ AUC ↓27%[1] EFV AUC ↓36%	Monitor anticonvulsant and EFV levels, or use alternative anticonvulsant[1]
	Δ NVP	No data but expected decrease in CBZ AUC	
Phenytoin	Δ EFV Δ NVP	Bidirectional induction of metabolism of both anticonvulsants and EFV / NVP.[1,26]	Monitor anticonvulsant and EFV / NVP levels and virologic response.[1]
Benzodiazepines			
Alprazolam Diazepam	Δ EFV Δ NVP	Potential decrease in alprazolam/diazepam exposure.[22]	Monitor clinical effect and withdrawal symptoms.
Lorazepam	Δ EFV Δ NVP	No interactions.[1]	May be safely coadministered.
Midazolam Triazolam	Δ EFV	Potential inhibition of midazolam/triazolam metabolism, hence increase risk of prolonged/increased sedation, confusion or respiratory depression.[1]	Single dose intravenous midazolam may be used; chronic midazolam/ triazolam administration (oral or IV) should be avoided. Use alternative agent (e.g. lorazepam).[1]
	Δ NVP	Potential decrease in midazolam/triazolam effect.[22]	Monitor clinical effect and withdrawal symptoms.

Concomitant Drug	NNRTI	Description of Interaction	Suggested Management
Hormonal Contraceptives			
Hormonal contraceptives	Δ EFV	No effect on ethinyl estradiol but reduced AUC of norgestromin and levonorgestrel by 64% and 82% respectively. Possible contraceptive failure.[23]	Use alternative/additional contraceptive methods. Transdermally applied oestrogens and progestagens which avoid the first pass effect may be less affected than oral agents by enzyme inducers. [25]
	Δ NVP	Ethinyl estradiol AUC ↓23% [24] Norethindrone AUC ↓18% [24] Possible contraceptive failure.	Use alternative/additional contraceptive methods.
HMG-CO A Reductase Inhibitors			
Atorvastatin	Δ EFV Δ NVP	Atorvastatin AUC ↓43% with EFV.[27] No data on NVP.	Monitor cholesterol levels and adjust statin dose if necessary.
Lovastatin	Δ EFV Δ NVP	Potential decrease in lovastatin concentrations.	Monitor cholesterol levels and adjust statin dose if necessary.
Pravastatin	Δ EFV ◊ NVP	Pravastatin AUC ↓40%with EFV. [27] No interaction with NVP.	Monitor cholesterol levels and adjust statin dose if necessary.
Rosuvastatin	◊ EFV ◊ NVP	No interaction.[1,28]	No dosage adjustment necessary.
Simvastatin	Δ EFV Δ NVP	Simvastatin AUC ↓60% with EFV.[27] No data with NVP.	Monitor cholesterol levels and adjust statin dose if necessary.
Oral Anticoagulant			
Warfarin	Δ EFV Δ NVP	Potential increase or decrease in warfarin concentrations.[1,8,29,30]	Monitor INR levels and adjust warfarin dose if necessary.

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Table 19 • Drug Interactions Between NRTIs and Other Drugs

Concomitant Drug	NRTI	Description of Interaction	Suggested Management
Antifungal			
Ganciclovir	Δ DDI	DDI AUC ↑100% [1,2]	Monitor for DDI associated toxicities.
	Δ AZT	AZT AUC ↑20% May increase hematological toxicity.	Monitor for AZT associated toxicities.
Ribavirin	• DDI	Increase exposure to DDI active metabolite and thus increase risk of toxicities (lactic acidosis, pancreatitis). [2,3,4]	Contraindicated- do not co administer. Fatal hepatic failure and other DDI-related toxicities reported with co-administration.
Ribavirin ± PEG IFN alpha	• AZT	Significant increased risk of anemia with co-administration.[5,6]	Avoid co-administration if possible or closely monitor virologic response and hematotoxiciy
Others			
Allopurinol	• DDI	DDI AUC ↑105% [2] Potential for increased DDI associated toxicities	Contraindicated–do not co administer.

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Table 20 • Drug Interactions Between Raltegravir (RAL) and Other Drugs

Concomitant Drug	Description of Interaction	Suggested Management
Antibacterials		
Δ Rifampicin (RIF)	RIF 600mg OD + RAL 400mg BD: RAL AUC ↓40% [1] Higher RAL resistance rates reported with RAL 400mg BD vs RAL 800mg BD[2]	Increase RAL to 800mg BD when used with rifampicin. (RAL AUC ↑27%)[1] Monitor efficacy and toxicity.
Antiviral		
Δ Atazanavir (ritonavir-boosted)	RAL AUC ↑41%[3] No observed increase in adverse effects	Monitor efficacy and toxicity.
Δ Efavirenz Acid Reducers	RAL AUC ↓36%[4] Not clinically significant effect	Monitor efficacy and toxicity.
Acid Reducers		
Δ Antacids	Coadministration of raltegravir with antacids containing divalent metal cations may reduce raltegravir absorption by chelation. Taking an aluminium and magnesium antacid within 2 hours of raltegravir administration decreased raltegravir trough concentrations by ~60% [5,6]	Do not coadminister. If needed, space administration by at least 2hr.
◊ All proton-pump inhibitors (e.g. omeprazole)	RAL AUC ↑37% No clinically significant effect [6,7]	No dosage adjustment needed.
◊ All H2-antagonists (e.g. Famotidine)	RAL AUC ↑44% No clinically significant effect [6]	No dosage adjustment needed.

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Introduction

TB is the commonest opportunistic infection among HIV patients and is a leading cause of HIV deaths. Treatment of TB coinfected HIV patients is complex and need to take into account timing of HAART, potential drug interactions between HAART and anti TB medications and IRIS. Collaboration between HIV and TB care services are recommended.

Role of Isoniazid Prophylaxis Therapy (IPT)

Isoniazid prophylaxis therapy for six months should be offered to all HIV patients once active TB has been ruled out.[1] Thus all patients with HIV need to be screened for active TB by using standard screening tool for TB.[2] IPT can reduce overall TB risk by 33%. Dose of Isoniazid is 10mg/kg and maximum 300mg daily.

Role of HAART in HIV individuals with TB

HAART during anti TB treatment reduces mortality and results in earlier sputum smear/ culture conversion. WHO recommends HAART in all TB / HIV coinfected patients regardless of CD4. However earlier HAART is not associated with reduction in deaths in patients with CD4>50 cells/ml if there is no evidence of serious HIV disease.[3,4] Deferral of HAART initiation until the maintenance phase of TB treatment may be warranted in the setting of HIV and CNS-TB coinfection, as early HAART treatment is associated with higher mortality.[5]

Recommendations of Initiating HAART in HIV Individuals with TB

CD4 Level	Recommendations
CD4 <50 cells/ml	Commence HAART within 2 weeks of intensive phase of TB treatment
CD4 >50 cells/ml	Commence HAART in maintenance phase of TB treatment unless there is evidence of serious HIV disease (ie low body mass index, anemia, hypoalbuminemia, organ system dysfunction)

Efavirenz is the preferred NNRTI in combination with 2 NRTI. Nevirapine is associated with higher rates of hepatotoxicity than efavirenz.[6] Nevirapine lead in dosing is not advised if commenced when patient is on TB treatment. Evidence suggests that TB patients on nevirapine based regimen showed a poorer virologic outcome compared to efavirenz based regimen.[7] However in a patient with suppressed viral load already on nevirapine based regimen, the same regimen may be continued.

If patient is intolerant to Efavirenz, Raltegravir based regimen is an option.[8] Use of PIs based regimen is not recommended due to drug-drug interaction with rifampicin in which PIs drug levels are reduced by more than 90%.[9]

Rifabutin as a substitution for rifampicin is recommended when PIs need to be used. The standard dose of rifabutin should be reduced to 150 mg daily or 300 mg three times/week when PIs are used.[10]

Recommended HAART Regimens in HIV Individuals with TB

Options	HAART regimens
Preferred	Efavirenz plus 2 NRTIs
Alternative	Raltegravir plus 2 NRTIs Nevirapine plus 2 NRTIs

Immune Reconstitution Inflammatory Syndrome (IRIS)

IRIS can occur 2-12 weeks after commencing HAART and is usually seen in patients with CD4<50, extrapulmonary TB and anemia.[11] IRIS usually manifests with fever and lymphadenopathy and is usually self limiting. HAART and AntiTB should not be ceased if IRIS occurs. In mild IRIS, non steroidal agents may be used. In serious IRIS there is a role for steroids.

Role of Cotrimoxazole in TB HIV Co-Infection

Cotrimoxazole prophylaxis should be given to all patients with TB infection throughout TB treatment. It should be initiated as soon as possible and continuation of cotrimoxazole after TB treatment depends on CD4 and VL.[12]

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MANAGEMENT OF HEPATITIS B AND HIV CO-INFECTION

The disease course of hepatitis B (HBV) infection is deleteriously affected by HIV co-infection. In Hepatitis B and HIV co-infection, ART should be initiated in all patients with CD4 <500

Effects of HIV on HBV Disease Progression

1. Lower spontaneous clearance of acute Hepatitis B infection
2. Higher HBV replication but lower transaminase levels in comparison to chronic HBV mono-infection
3. More rapid decline in Hepatitis B surface antibody (anti-HBs)
4. More episodes of reactivation especially in those who are positive for anti HBc antibody but negative for other markers of HBV infection
5. Lower seroconversion rates from HBeAg to anti-HBe antibody
6. Increased liver related mortality especially in those who are severely immunosuppressed (CD4 <100).
7. Less necro inflammatory activity on liver biopsies but more rapid progression to liver fibrosis, cirrhosis, end stage liver diseases and/or hepatocellular carcinoma.

Effects of ARVs on HBV

Chronic HBV does not substantially alter the progression of HIV infection or influence HIV suppression or CD4 response to cART.

Elevations in transaminase levels may be seen, that are ascribed to:

a. Hepatic flare due to immune reconstitution after initiation of antiretroviral therapy.
b. Discontinuation of ARV active against HIV and Hep B virus
c. ARV related toxicity

Pretreatment assessment for co-infected individuals

- Serum HBV-DNA viral load by PCR (Quantitative) -
- Staging of liver fibrosis by liver biopsy and/or fibroscan unless there is already clinical evidence of cirrhosis
- Cirrhotic patients require OGDS to look for evidence of varices. If varices are present primary prophylaxis with a beta blocker is required unless there is contraindication to its use in which case primary banding is to be considered. Patient without varices will need a repeat upper endoscopy in 2-3 year.
- Alfa-fetoprotein and ultrasound of liver should be repeated 6-12 monthly for all patients.

Treatment Recommendations for HBV and HIV Co-Infection

Co-infected patients should be advised:

- To abstain from alcohol
- To avoid smoking
- Receive hepatitis A vaccination if the patient is not immune to it.

Because of the negative effect of immune depletion on HBV progression, and the increased risk of liver-related deaths in patients with CD4 counts below 500 cells/mL patients should be treated with drugs active against both viruses.

In patients who are Hep B & HIV co-infected with CD4 >500, decision to start ART will depend on ALT, HbeAg status, HBV DNA levels and any evidence of liver cirrhosis. (please refer to algorithm for management)

Patients with ALT <2 ULN, who are HBeAg negative and whose HBV DNA is $<10^4$ copies/ml (2000 IU/ml) are unlikely to have active viral replication or active liver disease. Hence, anti-HBV therapy is not recommended.

However, ALT and HBV DNA need to be monitored regularly to assess Hep B reactivation.

ART must be started in all HIV/HBV co-infected individuals who require treatment for their HBV infection, irrespective of CD4 cell count or WHO clinical stage.

Antiretroviral regime which includes two active drugs against HBV and HIV is the preferred option.

The suggested ARV regime should consist of a combination of Tenofovir and Lamivudine (3TC) or Emtricitabine (TDF) as the NRTI backbone

The duration of treatment is lifelong.

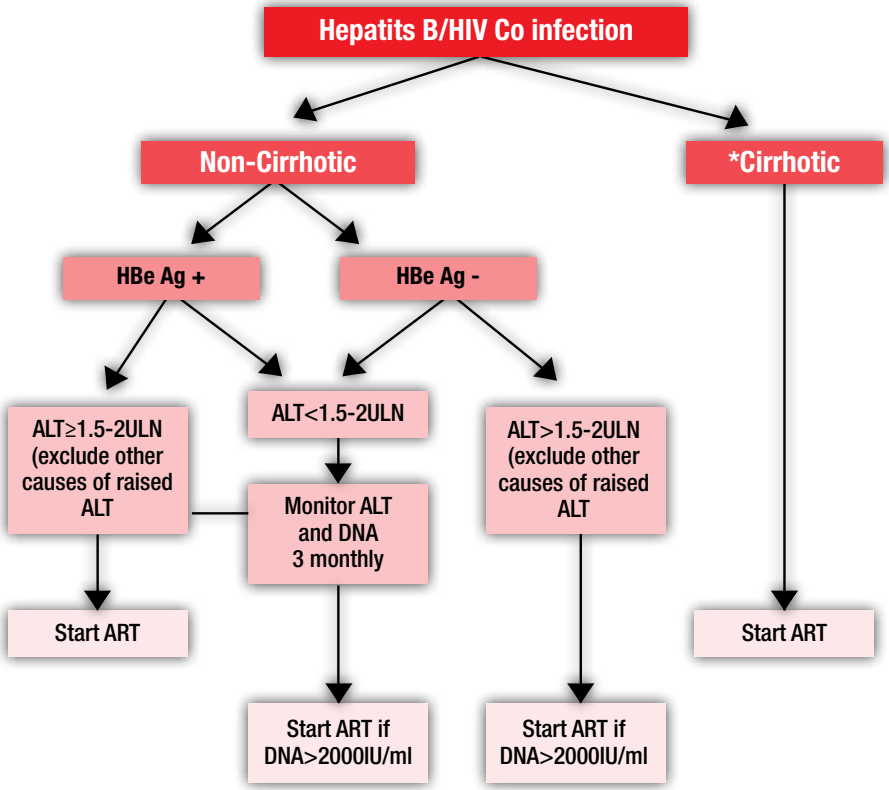
Patients with decompensated cirrhosis and evidence of HBV replication needs urgent treatment.

All patients should ideally be co-managed with a Gastroenterologist.

Those with ascites will need to have diagnostic paracentesis to exclude spontaneous bacterial peritonitis

If patient develops toxicity, decompensation or HBV drug resistance, refer and consult the Hepatologist / Gastroenterologist & ID physician.

Algorithm 1 • Treatment of HIV in Hepatits B and HIV Co-Infection Management with CD4 >500



* Cirrhosis is a chronic disease of the liver characterized by nodular liver surface, irregular margin and diffuse fibrosis which results in portal hypertension, hepatic insufficiency, jaundice and ascites. Cirrhosis can be confirmed by either ultrasound, fibroscan or biopsy

Introduction

Hepatitis C affects 5-15% of the 33 million people living with HIV worldwide and up to 90% of injecting drug users .[1,2] Liver disease has become a major cause of death in HIV infection and 66% are secondary to HCV .[3] Strategies to prevent, screen and treat HCV in people with HIV are becoming increasingly important.

Effects of HCV/HIV Co-Infection

Co-infected patients are less likely to clear HCV viremia following acute HCV infection and have higher HCV RNA viral loads. They also have more rapid progression of liver fibrosis which leads to a higher rate of end-stage liver disease and mortality.[4]

Effects of Antiretrovirals on HCV Infection

ART was associated with a decrease rate of liver fibrosis progression.[5] These patients are however at greater risk of ART induced hepatotoxicity.[6]

Goal of Treatment

Cure: Sustained Virological Response (SVR-undetectable HCV RNA 24 weeks after the end of therapy). This is associated with improved liver histology and decresed risk of progression to cirrhosis, end stage liver disease and hepatocellular carcinoma and death.[7]

Candidates Considered for HCV Treatment

Non cirrhotic or Child's grade A cirrhosis

CD4 count > 200 cells/ml

No underlying OIs

No contraindications for interferon and/or ribavarin therapy

Patients with psychiatric, opthalmologic, respiratory, cardiac or neurological illnesses should be on regular treatment and follow up from the respective subspecialities

Motivated patients keen for treatment and likely to stay on treatment and attend regular follow up

Negative TB workout for all patients (CXR, ESR +/- sputum)

Pretreatment Assessment

Diagnosis:

Anti-HCV antibody (if CD4 <100, HCV antibody is negative but HCV infection is suspected, HCV RNA is recommended)

HCV RNA Viral load

HCV genotype

Status of Liver Damage:

Stage fibrosis (FibroScan, liver biopsy)

Hepatic synthetic function (Liver function test, Coagulation test, Albumin)

Ultrasound of the Hepatobiliary system

Others:

Full blood count, renal profile, thyroid function test, alpha-feto protein (in cirrhotic patients)

Autoantibodies (Antinuclear antibody)

CD4 count

ECG

UFEME

Treatment Recommendation for HCV/HIV Co-Infection[8]

Abstain from alcohol

Hepatitis A and B vaccination if not immune

Those receiving ART and treatment for HCV require close monitoring because of potential drug-drug interactions and increased risk for drug toxicity.

Treatment of choice: [9,10]

Combination of pegylated interferon α (PEG-IFN) plus weight based ribavarin.

Duration of therapy may vary from 24 to 72 weeks depending on HCV Genotype.

Treatment should be discontinued if early virological response (EVR = 2 log reduction of HCV viral load) is not achieved at week 12.

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

Initiating ART should follow the same principles as in HIV monoinfection
Tenofovir + Lamivudine + Efavirenz
(OR)
Abacavir + Lamivudine + Efavirenz

Avoid:

Didanosine : risk of mitochondrial toxicity (lactic acidosis, acute pancreatitis)

Zidovudine : risk of anaemia

Stavudine : risk of mitochondrial toxicity (lactic acidosis, acute pancreatitis)

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Introduction

Definition of Couple
Two persons in an ongoing sexual relationship; each of these persons is referred to as a "partner" in the relationship.

Definition of Serodiscordant Couple
A couple in which one partner is HIV-positive and one partner is HIV-negative.

ART for prevention of transmission in the HIV positive partner who is eligible for ART treatment (CD4 <350 cells/µL)
- ART is strongly recommended as per our current CPG recommendations
- Partner who is started on ART for their own health should be informed that ART also reduce HIV transmission to their uninfected partner.
  **Strong recommendation, high quality evidence*

ART for prevention of transmission in the HIV positive partner with CD4 >350 cells/µL and who do not have clinical indications for treatment.
- ART should be considered and offered to reduce HIV transmission to uninfected partners.

**Strong recommendation, high quality evidence.*

The HPTN 052 randomized controlled trial found a 96% reduction in HIV transmission in serodiscordant couples where the partner with HIV with a CD4 count between 350 and 500 cells/µL had started ART early.[1] Treatment should be accompanied by counseling of the couple on the fact that ART is lifelong and the combination of treatment and consistent condom use is likely to offer greater protection than either one alone. The annual risk of transmission of HIV from an infected partner to an uninfected partner in a serodiscordant relationship can be reduced from 20–25% to 3–7% in programs where condom use is recommended for prevention.[2]

The benefits of commencing HAART in serodiscordant couple
1. To reduce the risk of HIV transmission to the seronegative partner.
2 To allow safer conception for serodiscordant couples who are having unprotected sex and who desire children. Risk of transmission is reduced for the uninfected partner which also protects the fetus from HIV infection.

1. It is possible for couples to remain serodiscordant indefinitely if they consistently practice safer sex using condoms.
2. Treatment for the HIV-positive partner also is highly effective in reducing the risk of transmission to the HIV-negative partner.
3. Combination of treatment and consistent condom use are likely to offer greater protection than either one alone.

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ANTIRETROVIRAL THERAPY FOR ILLICIT DRUG USERS

Introduction

Illicit drug users especially intravenous drug users (IDU) often have difficulties accessing HIV care. They are less likely to receive antiretroviral therapy compared to other populations.[1] Evidence indicate that IDUs benefit significantly from the treatment but mortality remains high compared to non-user HIV patients. Factors contributing to mortality include delayed initiation of treatment, poor adherence to treatment regimen, interruptions in medical care and ongoing drug use.

HIV Treatment Among Illicit Drug Users / IDUs

Available data indicates that, when not actively using illicit drugs, efficacy of antiretroviral therapies among IDUs is similar to other populations. Therapeutic failure in this population is related to the degree of drug use resulting in disruption of organized daily activities, rather than drug use per se.

Treatment of substance abuse is often a prerequisite for successful antiretroviral therapy.[2] Close collaboration with substance abuse treatment programs and proper support and attention to the needs of this population with good patient–clinical team relationships are critical components of successful HIV treatment.

For better management of drug-drug interactions in patients on antiretroviral treatment, there should be good communication between doctors running HIV clinics and those in the opioid substitution treatment clinics.

The clinical and CD4 criteria for initiating ART in substance-dependant patients are no different from other patients. Although not systematically studied, the apparent high incidence of ART-related toxicities is likely due to 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 pharmacologic treatment for opiate addiction. In opioid-dependent people, methadone prevents withdrawal symptoms without producing significant sedation or intoxication. It is the only drug approved as oral substitution therapy in the government hospitals/health centres. Pharmacokinetic interactions of antiretroviral (ARV) agents with methadone are challenges to successful therapy.

Co-administration of NRTI, NNRTI and PIs with Methadone can result in significant reduction in exposure to methadone and alteration in ARV serum levels, leading to opioid withdrawal symptoms or increasing ARV toxicities, which threatens ongoing adherence to therapy.[3]

Table 21 • Interactions of Clinical Significance Between Methadone and ART[4,5]

Antiretroviral Agent	Effect on Methadone	Methadone Effect on Antiretroviral Agent	Methadone Effect on Antiretroviral Agent Comment
Nucleoside / Nucleotide Reverse Transcriptase Inhibitors (NRTIs)			
Abacavir (ABC)	Methadone clearance ↑ 22%	Concentrations slightly decreased (but not clinically significant)	Patients should be monitored for methadone withdrawal symptoms; dose increase unlikely, but may be required in a small number of patients
Didanosine (ddI)	None	Buffered ddI concentration decreased by 57%	Buffered ddI dose increase may be considered or use EC ddI instead
		EC ddI unchanged	
Emtricitabine (FTC)	No data	No data	
Lamivudine (3TC)	None	None	No dose adjustment necessary
Stavudine (d4T)	None	Reduces stavudine AUC and Cmax by ↓23% and 44% respectively	The clinical significance of a change in drug exposure of this magnitude is not certain
Tenofovir (TDF)	None	None	No dose adjustment necessary
Zidovudine (AZT)	None	Zidovudine AUC ↑ 29–43%	Monitor for AZT adverse effects, in particular bone marrow suppression (especially anaemia).
Non-nucleoside Reverse Transcriptase Inhibitors (NNRTIs)			
Efavirenz (EFV)	Methadone Cmax ↓ 45% and AUC ↓ 52%	None	Symptoms of withdrawal may develop after 3–7 days, requiring significant increases in the methadone dose
Etravirine TMC-125)	None	None	No dose adjustment necessary
Nevirapine (NVP)	Methadone AUC ↓ 41%	None	Withdrawal symptoms frequent; generally occurring between 4 and 8 days after starting nevirapine; in case series of chronic methadone recipients initiating nevirapine, 50–100% increases in the daily methadone doses were required to treat opiate withdrawal

Antiretroviral Agent	Effect on Methadone	Methadone effect on Antiretroviral Agent	Methadone Effect on Antiretroviral Agent Comment
Protease Inhibitors (PIs)			
tazanavir (ATV)	None	None	If boosted with ritonavir, Methadone AUC ↓ 16%–18%; Opioid withdrawal unlikely but may occur. Adjustment of methadone dose usually not required; however monitor for opioid withdrawal and increase methadone dose as clinically indicated.
Darunavir (DRV)	None	None	
Indinavir (IDV)	None	None	
Lopinavir / ritonavir (LPV/r)	None	None	Opioid withdrawal unlikely but may occur. Adjustment of methadone dose usually not required; however, monitor for opioid withdrawal and increase methadone dose as clinically indicated.
Integrase Inhibitors			
Maraviroc (MRV)	No data–potentially safe	No data – potentially safe	
Raltegravir (RAL)	None	None	No dose adjustment necessary.

Buprenorphine and Antiretroviral Therapy

Buprenorphine is a potent synthetic partial opioid agonist with high receptor affinity and slow receptor dissociation. The potential advantage of buprenorphine is that it has a good margin of safety. This margin of safety also allows higher doses to be used for the purpose of prolonging action, without significantly increasing the opioid effect. In this way a double dose of buprenorphine can be given every second day, with no dose in between.

Table 22 • Interactions of Clinical Significance Between Buprenorphine and ART [4,5]

Antiretroviral Agent	Effect on Burprenorphine	Methadone Effect on Antiretroviral Agent	Methadone Effect on Antiretroviral Agent Comment
Nucleoside / Nucleotide Reverse Transcriptase Inhibitors (NRTIs)			
Abacavir (ABC)	Unknown	Unknown	Potential interaction that may require close monitoring,alteration of drug dosage or timing of administration
Didanosine (ddI)	None	None	No dosage adjustment necessary.
Emtricitabine (FTC)	No data	No data	—
Lamivudine (3TC)	None	None	No dosage adjustment necessary.
Stavudine (d4T)	No data	No data	—
Tenofovir (TDF)	None	None	No dosage adjustment necessary.
Zidovudine (AZT)	None	None	No dosage adjustment necessary.
Non-nucleoside Reverse Transcriptase Inhibitors (NNRTIs)			
Efavirenz (EFV)	Buprenorphine AUC ↓ 50%; norbuprenorphinea AUC ↓ 71%	None	No withdrawal symptoms reported. No dosage adjustment recommended; however, monitor for withdrawal symptoms.
Etravirine (TMC-125)	Buprenorphine AUC ↓ 25%	None	No dosage adjustment necessary.
Nevirapine (NVP)	None	None	No dosage adjustment necessary.
Protease Inhibitors (PIs)			
Atazanavir (ATV)	Buprenorphine AUC ↑ 93%; norbuprenorphine AUC ↑ 76%	↓ ATV levels possible	Do not co-administer buprenorphine with unboosted ATV.
Atazanavir (ATV) / ritonavir	Buprenorphine AUC ↑ 66%; norbuprenorphine AUC ↑ 105%	None	Monitor for sedation. Buprenorphine dose reduction may be necessary.
Darunavir (DRV) / ritonavir	Buprenorphine: no significant effect; norbuprenorphine AUC ↑ 46% and Cmin ↑ 71%	None	No dose adjustment necessary.

Antiretroviral Agent	Effect on Burprenorphine	Methadone Effect on Antiretroviral Agent	Methadone Effect on Antiretroviral Agent Comment
Protease Inhibitors (PIs) [con't]			
Lopinavir / ritonavir (LPV/r)	None	None	No dose adjustment necessary.
Ritonavir (RTV)	Potential for increased buprenorphine effects	No data	Observe; buprenorphine dose reduction may be necessary
Integrase Inhibitors			
Maraviroc (MRV)	No data–potentially safe	No data–potentially safe	No dose adjustment necessary.
Raltegravir (RAL)	No data–potentially safe	No data–potentially safe	Observe; buprenorphine dose reduction may be necessary

Subuxone (Buprenorphine/Naloxone) and Antiretroviral Therapy

Buprenorphine–naloxone combines the partial agonist buprenorphine with the opioid antagonist naloxone in a 4:1 ratio. The addition of naloxone deters the abuse by injection of buprenorphine.

Subuxone is becoming a popular oral substitution therapy and is available in this country. Naloxone does not have any significant drug interaction with any antiretroviral drugs. Thus, recommendations for buprenorphine and ARVs can be applied when subuxone is used concomitantly with ARVs.

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POSTEXPOSURE PROPHYLAXIS (PEP) FOR HIV INFECTION FOLLOWING OCCUPATIONAL EXPOSURES

The most common occupational exposure to HIV amongst health care worker (HCW) is needle stick or sharps injuries. In Malaysia, the Occupational Health Unit in the Ministry of Health has reported an incidence rate of 6.3 needle stick injuries per 1,000 HCWs in 2013.

Risk for Occupational Transmission of HIV to HCWs

Prospective studies of HCWs have estimated that the average risk for HIV transmission after a percutaneous exposure to HIV-infected blood is approximately 0.3% or 1 in 300 (95% CI=0.2-0.5%) and 0.09% or 9 in 10 000 (95% CI=0.0006-0.5%) after mucous membrane exposure (CDC 1991). The risk of exposure to fluids or tissue has not been quantified but is probably lower than that of HIV-infected blood exposures.

Factors that may increase the risk of HIV transmission include,

- **High viral load.** Risk of transmission from a HIV patient with undetectable serum viral load is thought to be low.
- **Deep injury with hollow bore needle.**
- **Type of body fluid**
- **Advanced HIV infection in the source patient**

Although there are concerns about HIV transmission from a source who is HIV-positive but in the "window period" before seroconversion, no such occupational transmission has occurred in the United States to date. There are also concerns regarding requests for PEP after percutaneous injuries from discarded needles. However no HIV infections from such injuries have been documented.

High Risk Body Fluids

Blood or visibly bloody fluids and other potentially infectious material (OPIM) (e.g., semen; vaginal secretions; breast milk; and cerebrospinal, synovial, pleural, peritoneal, pericardial, and amniotic fluids) are the only source fluids that carry significant risk. Exposure to non-bloody saliva, tears, sweat, nasal secretions, vomitus, urine or feces does not require PEP.

Exposures for Which PEP is Indicated:

- Percutaneous Exposure: Breach of skin by a sharp object (hollow-bore, solid-bore, cutting needles or broken glassware) that is contaminated with blood, visibly bloody fluid or OPIM or that has been from the source patient's blood vessel.
- Bite from a patient with visible bleeding in the mouth that causes bleeding in the exposed worker.
- Splash of blood, visibly bloody fluid or OPIM to a mucosal surface (mouth , nose or eyes)
- Exposure of non-intact skin (eg dermatitis, chapped skin, abrasion or open wound) to blood, visibly bloody fluid or OPIM.

Immediate Management

Exposed body sites to blood and potentially infectious fluid should be cleansed immediately. Exposed mucous membranes should be flushed with water liberally. Wound and skin exposure sites should be washed with soap and water. Squeezing the wound is not recommended as it may promote hyperemia and inflammation at the wound site, potentially increasing systemic exposure to HIV if present in the contaminating fluid. Alcohol, hydrogen peroxide, betadine or other chemical cleansers are best avoided.

HIV Status of the Source Patient:

If the HIV status of the source patient is not immediately available or complete evaluation of the exposure cannot be completed within 2 hours of the exposure, PEP with a two-drug regime must be immediately initiated while awaiting final decision.

If the HIV status of the source patient is unknown, consent for voluntary HIV testing of the source patient has to be obtained. HIV testing using rapid tests is strongly recommended for the source patient. Results obtained using HIV rapid test kits can be used to decide on PEP for HCWs, however all positive rapid tests should be confirmed by confirmatory tests as soon as possible.

If the source patient's rapid HIV test result is negative, but there has been history of high risk exposure in the previous 6 weeks, possibility of the source patient being in the "window period" must be considered. In such a situation, initiate PEP and discuss with Infectious Diseases Physician on additional testing to confirm infection.

If the source patient is known to be HIV-infected, the choice of PEP will depend on his current HIV viral load, his antiretroviral treatment history and previous resistance testing results. Do not delay the first dose of PEP while waiting for these information. Consult an Infectious Diseases Physician.

HIV Status of the Exposed HCW:

Baseline testing of the health care worker has to be done to identify those who were already infected at the time of exposure. In the rare event of seroconversion, following an occupational exposure, a negative baseline test is the only way to document that the HCW was infected as a result of the exposure.

PEP Recommendation When Exposed to HIV Positive Source Patient

Type of exposure with known HIV positive patient	PEP recommendation	
	Source already on HIV treatment and recent viral load is undetectable**	Source not on treatment or on HIV treatment but recent viral load is still detectable** or no recent viral load
* Needle stick injury or other sharps exposure	2 drugs	3 drugs
Mucous membrane or non-intact skin exposure	Consider 2 drugs	3 drugs

* penetrating injury to the skin with a sharp instrument containing fresh blood
** with our current HIV viral load assay, this will be < 20copies/ml

PEP Recommendation When Exposed to a Person of Unknown Status or to an unknown Source

As far as possible every effort must be made to track the source patient and check his or her HIV status. The decision to give PEP in such a situation has to be individualized depending on the HIV risk profile of the patient.

If source is unknown (eg. pricked by a needle in a general waste bin) the decision to give PEP should again be individualized depending on HIV risk profile of the patients in the area in which the needle was found and the likelihood of the sharp having been used recently. The needle however should not be sent for HIV testing.

Which ARV drug regime to use?

ARVs used in PEP	
2 drug regime	Add for 3 drug regime
Preferred Tenofovir* 300mg od + Emtricitabine* 200mg od Alternative Zidovudine 300mg bd + Lamivudine* 150mg bd	Preferred Raltegravir 400mg bd Alternative Lopinavir/Ritonavir 2 tab BD

* Requires dose adjustments if baseline creatinine clearance is <50mL/min
Tenofovir should be used with caution in those with renal insufficiency or taking other nephrotoxic drugs

In case of non-availability of the 3rd agent, a 2-drug ARV regimen (ie Tenofovir + Emtricitabine OR Zidovudine + Lamivudine) should be started as soon as possible.

Timing of Initiation of PEP:

All efforts has to be made to initiate PEP as soon as possible, preferably within 2 hours of exposure. Animal studies have shown that PEP is most likely to be effective when initiated within 24-36 hours. Time duration beyond which PEP should not be administered is not certain. Decisions regarding PEP beyond 36 hours should be made on a case-by-case basis.

Duration of PEP:

Duration : 28 days. Emphasis on adherence to treatment and completion of the course is important to achieve PEP effectiveness. A proactive approach to managing adverse effects will ensure HCWs adhere to PEP.

Recommended Follow Up of HCW

All health care workers receiving PEP should be re-evaluated within 3 days of the exposure. This allows for further clarification of the nature of the exposure, review of available source patient data, and evaluation of adherence to and toxicities associated with the PEP regimen. The exposed worker should be evaluated weekly while receiving PEP to assess treatment adherence, side effects of treatment and emotional status.

During the 12 week Follow Up Period, HIV-Exposed HCWs Should Be Advised to

- Use condoms to prevent potential sexual transmission
- Avoid pregnancy and breast feeding
- Refrain from donating blood, plasma, organs, tissue or semen.

HIV testing should be repeated at 4 weeks, and 12 weeks after exposure. It is recommended that other blood borne diseases such as Hepatitis B and C screening also be repeated at the same time.

Monitoring After Initiation of PEP						
	Baseline	**1st week**	**2nd week**	**3rd week**	**4th week**	**12th week**
Clinic visit	X	X Or by telephone	X Or by telephone	X Or by telephone	X Or by telephone	X Or by telephone
Monitoring blood tests	FBC, RP LFT		FBC (if on zidovudine)		FBC (if on zidovudine), RP, LFT	
HIV test	X				X	X

Responsibilities of Hospital Administrators

All hospitals must have a comprehensive plan to manage exposed HCWs. The plan must include details of

- who will perform counseling and post-exposure evaluation to determine the need for PEP during and after office hours,
- how ARVs needed for PEP will be made available within 2 hours of an exposure during and after office hours,
- how a 3-5 day supply of PEP will be made available for use especially on weekends and public holidays,
- who will pay for the ARV drugs.

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 diarrhea 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 inflammatory 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 tumour
Invasive cervical carcinoma
Atypical disseminated leishmaniasis
Symptomatic HIV-associated nephropathy or HIV-associated cardiomyopathy

Source: Revised WHO clinical staging and immunological classification of HIV and case definition of HIV for surveillance.2006
* added in the regional classification 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 1 • Dosage, Food Interaction, Storage And Adjustments In Hepatic Insufficiency

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 insufficiency[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
Tenafor (TDF)	300 mg daily Take without regard to meals

Generic Name	Dose	
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 insufficiency[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 insufficiency	
Lopinavir/ritonavir (LPV/r)	Tablet (heat-stable formulation)	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 Tablet (heat-stable formulation) is the preferred choice Refrigerate for long-term storage of capsule formulation (At room temperature: stable for 30 days)	
Integrase Inhibitor		
Raltegravir	400 mg twice daily	

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 • Dosage Adjustment for ARTS 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 (Crcl) Ml/MIN			Hemodialysis, CAPD	Comments & Dosage for CRRT
LAMIVUDINE	>50 - 90 300mg q24h	10 - 50 50-150mg q24h	<10 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; AD CAPD: no data	CRRT: full dose
TENOFOVIR	300mg q24h	300mg H 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: Hemodialysis; CAPD: chronic ambulatory peritoneal dialysis; ESRF: End stage renal failure

List of ARVs with No Dosage Adjustment with Renal Insufficiency

Efavirenz	Darunavir
Abacavir	Saquinavir
Atazanavir	Indinavir
Lopinavir	Raltegravir

Annex 5 • Severity Grading

SOURCE: Division of AIDS, National Institute of Allergy and Infectious Diseases, USA – modified

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; significant assistance required; significant medical intervention / therapy required; hospitalization or hospice care.

	Grade 1	Grade 2	Grade 3	Grade 4
Hemoglobin	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 without 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

Abbreviations

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

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