Consensus Guidelines on Antiretroviral Therapy 2016

(Draft document)

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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
nPEP non-occupational postexposure prophylaxis
NNRTI non-nucleoside reverse transcriptase inhibitor
NRTI nucleoside reverse transcriptase inhibitor
NVP nevirapine
PI protease inhibitor
PrEP preexposure prophylaxis
PLCS prelabour caesarian section
RPV rilpivirine
RTV ritonavir
STI sexually transmitted infection
TB tuberculosis
TDF tenofovir disoproxil fumarate
VL viral load

Chapter 1 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.

For this interim update of "Consensus Guidelines on Antiretroviral Therapy", the contributors reviewed and updated some of the chapters based on the current information and two new chapters about nPEP and PrEP had been included.

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 those are available
4. Underlying medical diseases e.g. cardiovascular disease, diabetes mellitus, hyperlipidemia, depression etc.
5. Possible drug-drug interactions, dosing frequency and pill burden
6. Risk of primary resistance e.g. acquisition of HIV from a partner who is already on treatment
7. Individual factors that may hinder adherence e.g. irregular working hours, social support etc.

Goals and Benefits of Antiretroviral Therapy

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

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

Antiretroviral (ARV) drugs in Malaysia

Antiretroviral therapy (ART) 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 1.0 Antiretroviral (ARV) drugs in Malaysia

Nucleoside Reverse Transcriptase Inhibitors (NRTI) / Nucleotide Reverse Transcriptase Inhibitors (ntRTI)	Abacavir (ABC) Lamivudine (3Tc) Abacavir/Lamivudine (combination pill) Tenofovir (TDF) Tenofovir (TDF)/Emtricitabine (FTC)(combination pill) Zidovudine (AZT) Zidovudine (AZT)/Lamivudine (3TC) (combination pill)
Non-Nucleoside Reverse Transcriptase Inhibitor (NNRTI)	Efavirenz (EFV) Nevirapine (NVP) Etravirine (ETV) Rilpivirin (RPV)
Protease inhibitor (PI)	Atazanavir (ATV) Ritonavir (RTV) Darunavir (DRV) Lopinavir / ritonavir (LPV/r)
Integrase Inhibitors	Raltegravir
CCR5 Antagonist	Maraviroc
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

mosteffective dosages according to published data. Dosing simplification will improve adherence andmaintain durable virological suppression.[1, 2]

Table 1.2 Fixed Dose Combinations Registered in Malaysia

Abacavir / lamivudine
Tenofovir / emtricitabine
Zidovudine / lamivudine
Abacavir / lamivudine / zidovudine (Trizivir)
Lopinavir / ritonavir (LPV/r)

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Chapter 2 Assessment of Adults with HIV Infection

I. Initial assessment and management of newly diagnosed patients.
II. A thorough history is mandatory for all patients with HIV infection**.**
III. A complete physical examination is mandatory for ALL patients with HIV to look for signs related to AIDS and opportunistic infections.
IV. Laboratory testing for initial evaluation AND monitoring during follow-up.

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]

Table 2.0 History Taking for a HIV Positive Patient[3]

	Symptoms/ components	**Significance**
History of Presenting Complaint	Fever, Cough, Dyspnea, Diarrhea, constitutional symptoms.	Diagnosis of opportunistic infections.
	Lethargy, weakness, weight loss, forgetfulness	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 and current medical history	TB, hepatitis, herpes, varicella (Syphilis, gonorrhea, Chlamydia) DM, IHD, HPT, Renal disorder, dyslipidemia. Treatment received or completed for the above. Vaccinations Last negative HIV test.	Risk of worsening condition due to ARVs.
Psychosocial History	Circle of confidentiality	

	Partner & Children Support network Occupation, housing, mental health issues	
Sexual & Sexual Reproductive History	Sexual history & practices Safer sex & risk reduction Partner status & disclosure issue	PMTCT prophylaxis. Transmission prevention measures.

Table 2.1 Important Laboratory Investigations

Evaluation	Investigations	Specific Tests	Entry to Care	Pre- ART	At Follow-up On ART	Comments
HIV Disease	All referred cases of HIV infection need a confirmatory test.					
	Plasma HIV RNA	HIV viral load	See com ment	x	4-6 months after initiation of ART. Annualy if stable	Not for routine baseline if resources are limited
	CD4		√	√	Refer section 2.1	
Co infection	Syphilis serology	VDRL/RPR/TPHA	√	**x**	Annual screening if at risk.	Consider more frequent
	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 antibody (HBc Ab total) if Hep Bs Ag negative and Liver function abnormal. Measure HCV RNA if HCV antibody positive or acute infection suspected.
	Hep C Serology	HCV Antibody	√	**x**	Annual screening If at risk	
CXR			√	**x**	When clinically indicated	To look for active TB (consider IPT)
Hematology	FBC		√	√	Every 4 to 6 months (only if patient is on AZT or symptomatic)	If on AZT – before initiation and at week-4, 8 & 12 or symptomatic
CVS	ECG		√	If on PIs	When clinically indicated	If patient has other risk factors for IHD
Metabolic	Fasting lipid profile		√	**x**	Every 6 to 12 months [1]	EFV, NRTIs, PIs (with exception of unboosted atazanavir), may lead to insulin resistance and dyslipidaemia.
	Fasting blood sugar		√	**x**	Annually if initial screening results are normal 3–6 monthly if prediabetes is detected[4]	
Liver	ALP, AST ALT, Bilirubin, Albumin		√	√	Every 4 to 6 months	NRTI and NNRTI drugs cause hepatotoxicity. If on NVP, ALT need to be monitored more frequently; at baseline, 2, 4, 12 weeks, then every 3-6 months Obtain ALT in patients with new onset of rash
Renal	Renal function test/ eGFR		√	√	At week 4, 8 and 12 upon initiation of	TDF may cause renal tubular dysfunction.

					Tenofovir (TDF) 4 to 6 monthly if stable	Routine monitoring of calculated creatinine clearance should be performed for all patients on TDF during follow up
	Dipstick		√	If clinically indicated		
Others	Serum lactate		**x**	**x**	As clinically indicated	Lactic acidosis is a rare complication of NRTI due to mitochondrial dysfunction.
	Cervical PAP smear for women	Pap smear	√		Annualy, if the results of the 3 consecutive Pap tests are normal, follow up Pap tests should be every 3 years [3]	

2.1 Monitoring While on Antiretroviral Therapy (refer Table 2.1)

CD4 Count:
Successful therapy is defined as an increment in CD4 cell count that averages 100 – 150cells/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 and CD4 counts >350 cells/mm^3 on 2 occasions 6 months apart, further repeat of CD4 count is not needed.[2](Unless treatment failure is suspected)

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.

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.

2.3 Co-Trimoxazole Preventive Prophylaxis

Co-trimoxazole is recommended for Pneumocystis jiroveci pneumonia (PJP) prophylaxis to all susceptible individuals as it has been shown to decrease the risk of PJP by nine fold in this population.[6]

Table 2.2 PJP Prophylaxis

When to start	What to start	When to stop
1. CD4 count of <200/µL or CD4 percentage of <14% 2. Oropharyngeal candidiasis 3. Opportunistic infections /AIDS defining illness 4. Patient who has than successfully completed PJP treatment	One double-strength (DS) tablet or two single-strength readings (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 AND HIV-VL is undetectable more than once

Co-Trimoxazole in Pregnant / Lactating Women
Women who fulfill 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 2.3 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.

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Chapter 3 Optimizing Care and Maximizing Benefits of ART

3.1 PRE ART CAUNSELLING

Currently, first line HAART offers the best opportunity for effective viral suppression and immune recovery. It also improves mortality as it improves AIDS related and non AIDS related serious illnesses. PLWH should be given opportunity in making decisions about their treatment .Studies shows that good quality relationship and good communication skills between clinician and PLWH are associated with better treatment outcome.
Before prescribing ART, clinician should assess individuals:

1. Understanding of general knowledge on HIV, ART and their potential side effect.
2. Perception of personal need of ART
3. Readiness to start therapy including timing and dosing regime
4. Willingness to adhere to lifelong therapy.
5. Psychological and neurocognitive issues that could impact on adherence.
6. Socio economic factors that could impact on adherence including but not limited to poverty, family support, housing, domestic violence, Immigration status and intravenous drug user.
7. Future parenting and pregnancy plan.
8. Future follow up and monitoring plan including educating them on the expected clinical, virological and immunological response.

Moreover, community advocacy and peer support group including clinic-based peer support are helpful in supporting patient's understanding and confidence on treatment and may also help to increase readiness to start treatment. Wide range of Information on disease and treatment can be made readily assessable to PLWH in community services, clinics, peer –support services and online website.

3.2 ART 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 occurrence of IRIS after starting HAART

3.3 ADHERENCE TO ART

ART adherence is the key to successful HIV treatment. Current data shows that to maintain successful viral suppression, 95% or more adherences to ART is required. Failure rate will rise as adherence rates deceases and this will lead to negative implication on patient's health, disease progression and public health intervention to reduce transmission.

Specific group of population are at risk of poor adherence which includes those with poor family support, intravenous drug users, adolescence and pregnant mothers. Interventions to improve adherence are most likely to be successful when they are comprehensive and tailored to individual's socio-demographics background and behavioural characteristic. Therefore, method of counselling on improvement of adherence must always be individualized**.**

3.3.1 Interventions to Improve Adherence

Before writing the first prescriptions, the clinician should assess the patient's readiness to take medication, including information such as 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 3.0 Strategies to Improve Adherence to Antiretroviral Therapy

Strategies	**Examples**
Multidisciplinary team approach	Provide an accessible, trusting relationship between the patients and physicians, nurse counsellors, family members, social workers, peer support group and pharmacists.
Establish patient readiness to start ART	• Assess patient's attitude and belief regarding ART and adherence • Practice adherence to planned ART regime using 'vitamin training' • Pill organizers and medication reminder aids (e.g. alarm clock using mobile phone) • Review source of social support (positive and negative) and discuss ways to enhance support for adherence
Assess and simplify the regimen	• Preferably once a day regime

Identify potential barriers to adherence	• Psychosocial issues (e.g. housing problems, legal issues, disrupted family) • Active substance abuse or at high risk of relapse • Low literacy • Busy daily schedule and/or travel away from home • Nondisclosure of HIV diagnosis – the need of 'treatment buddy' • Scepticism about ART • Lack of continuous access to medication
Provide resources for the patient	• Referrals for mental health and/or substance abuse treatment • Continuous pill supply - e.g. SPUB "Sistem pendispensan ubat bersepadu" to nearest government clinic, postage of medication to patient's home, pre-packaged medications – 'drive-through counter' • 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 non-adherence	• Failure to fill the prescription(s) • Failure to take the right dose(s) at the right time(s)
Identify reasons for non-adherence	• 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

3.4 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

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 tests 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 does not 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)

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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Chapter 4 When to Start ARTs

4.1 When to start ARTs

Target population	Specific recommendation
Adults (≥18years)	• Antiretroviral therapy (ART) is recommended for all HIV-infected individuals, regardless of CD4 count, to reduce the morbidity and mortality associated with HIV infection. • ART is also recommended for HIV-infected individuals to prevent HIV transmission.
	As a priority, ART should be initiated in : • All adults with severe or advanced HIV clinical disease (WHO clinical stage 3 or 4) • Individuals with CD4 count≤350 cells/mm3 • HIV-associated nephropathy (HIVAN) • HIV/hepatitis B virus co-infection • HIV/hepatitis C virus co-infection
Pregnant and breastfeeding women	ART should be initiated in all pregnant and breastfeeding women living with HIV at any CD4 cell count and continued lifelong.

(Adapted from Guidelines on When to Start Anti Retroviral Therapy and Pre Exposure Prophylaxis for HIV, WHO September 2015)

On a case-by-case basis, ART may be deferred because of clinical and/or psychosocial factors; however, therapy should be initiated as soon as possible.

4.2 When to start ART after 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]

ART is recommended in all HIV-infected persons with TB. For ART-naive patients, ART should be started within 2 weeks when the CD4 count is <50 cells/mm3 and by 8 to 12 weeks for all others. In patients with TB meningitis and low CD4 cell counts, early ART may pose a risk that calls for careful monitoring and consultation with experts

In patients with cryptococcal meningitis, it is prudent to delay initiation of ART at least until after completion of antifungal induction therapy (the first 2 weeks) and possibly until the total induction/consolidation phase (10 weeks) has been completed. Delay in ART may be particularly important in those with evidence of increased intracranial pressure or in those with low CSF white blood cell counts. Hence, the timing of ART administration should be

considered between 2 and 10 weeks after the start of antifungal therapy with the precise starting dates based on individual conditions and local experience. If effective ART is to begin prior to 10 weeks, the treating physicians should be prepared to aggressively address complications caused by IRIS, such as elevated intracranial pressure (ICP).

For other forms of cryptococcosis, where the risk of IRIS appears to be much lower, the optimal time to begin ART and antifungal therapy is not clear. However, it would seem prudent to delay initiation of ART by 2 to 4 weeks after starting antifungal therapy.

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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Chapter 5 Principle of Selecting First Line ART

2NRTI+1NNRTI are the preferred option.

Table 5.0 Preferred and alternative ART options

Adult	**Preferred first line** TDF+FTC+EFV	**Alternatives** AZT+3TC+EFV(or NVP) ABC+3TC+EFV(or NVP) TDF+FTC+NVP
	TDF+FTC+Raltegravir (if intolerant of NNRTI)	ATV/r +TDF/FTC LPV/r+TDF/FTC

Considerations prior to starting treatment

The following factors should be considered to determine which ART regimen is the best for a particular patient:

- Co-morbids and organ dysfunction(e.g. renal insufficiency, Hepatitis B co-infection, anemia, psychiatric conditions, heart disease, TB)
- Impact of regimen itself(e.g. pill burden, pill size, potential for drug interactions, anticipated side effects, food/ fasting requirements)

NRTI

TDF and AZT generally are comparable in terms of efficacy[1], however some studies have shown better efficacy and less side effects with TDF based therapy compared to AZT. The use of d4T is discouraged. For patients who are started on d4T, they should be switched to TDF or AZT after the first 6 months to avoid its long term side effects.

TDF should be avoided in patients with chronic kidney disease with CrCl<50ml/min.[2] TDF preferred in patients with Hepatitis B co-infection.[3]

AZT should not be initiated in patients with baseline hemoglobin<8.0g/dL.

Abacavir(ABC) may be considered in special circumstances where the preferred regimens are not suitable because of toxicities or anticipated drug-drug interactions. However, ABC is not recommended in cases where HIV viral load is > 100,000 copies/ml.[4]

NNRTI

NVP and EFV have comparable clinical efficacy when used in combination ART. However, NVP is associated with higher risk of rash, Steven-Johnson Syndrome and hepatotoxcity compared to EFV.[5]In case of severe hepatotoxicity or skin reactions, NVP should be permanently discontinued. NVP must be avoided in women with CD4 count >250 and men with baseline CD count >400 due to significant increase in incidence of symptomatic hepatic events. Lead in dosing for 2 weeks for NVP is suggested to decrease risk of hepatitis and rash.

EFV is the NNRTI of choice in individuals with TB/HIV co-infection who are receiving rifampicin-based TB treatment.[3]EFV should be avoided in patients with severe psychiatry illness and if their daily functional status is affected by its side effects.

NNRTI has low genetic barrier to resistance with long half lives. Abrupt discontinuation of NNRTI can lead to periods of NNRTI monotherapy with risk of resistance. Hence, when NNRTI is stopped, the backbone NRTIs should be continued for another 1 week before stopping all drugs.

INSTI and PI/r

Integrase strand transfer inhibitors (INSTI) or protease inhibitors (PI) may be considered as third agent in first line ART regime if patient is unable to tolerate the side effects of NNRTI.

Patients who are unable to tolerate ART or develop adverse reactions to ART should be referred to infectious disease physicians.

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Chapter 6 Management of treatment failure: after first line treatment

6.1 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 virological 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 200copies/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
The viral load level to define virologic failureis not fully agreed on worldwide. 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 regiment.

Diagnosing 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.

6.2 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 TDF or ABC for AZT-related gastrointestinal symptoms or anemia; change to NVP for EFV-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.

Clinical Scenarios in detectable viral loads.

- 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 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.

6.3 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.

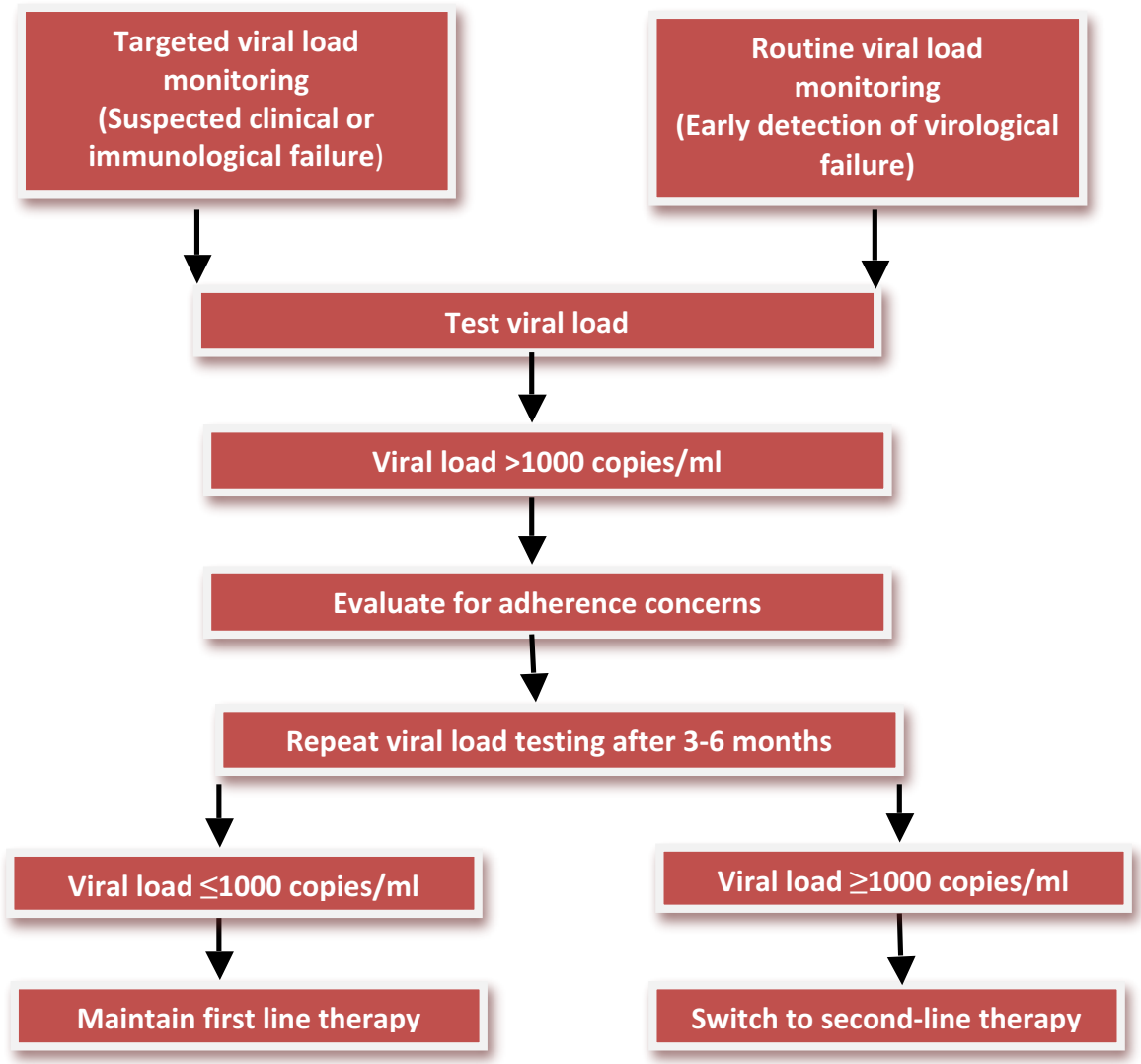
b. Ideally the new regimen should consist of at least 2, and preferably 3 fully active agents from at least one new class[5]

c. In general, adding a single, fully active antiretroviral drug in a new 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 decide to switch.

Fig 6.1 Viral load testing strategies to detect or confirm treatment failure and switch ART regimen in adults and adolescents



(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 3TC with AZT, d4T or TDF) fails, predicted resistance will be towards 3TC(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 6.0 Recommended second line regime[1]

Failing first line ART regime	Recommended second line ART regime		
	NRTI *	PI	Integrase inhibitors
AZT/D4T + 3TC + NNRTI	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 (e.g. concomitant renal failure that precludes use of TDF or a past history of anemia 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.

***Lopinavir/Ritonovir (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**.**

6.4 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 failing patient with no other ART 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 than 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].**

6.5 Viral Resistance Testing

Genotypic assays detect drug resistance mutations present in relevant viral genes. This test is not widely available at this time.Testing is usually not routinely necessary in first line failures if there has been no change in NRTIs while the viral loads were high.

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.

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Chapter 7 Prevention of mother-to-child Transmission

7.1 Introduction

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

Ideally ART should be started at 14 weeks of pregnancy. Women who present after 28 weeks must commence ART without delay. ID Physician should be consulted regarding the choice of ART regimen in these late presenting women. There is increasing evidence to support the use of ART regimen that includes Raltegravir in late presenting women to achieve more rapid viral load suppression and further reduce the risk of perinatal HIV transmission.[2, 3] Strict adherence to ART must be stressed throughout the pregnancy.

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

7.2 Pregnant women who are ART naïve

Table 7.0 presenting CD4 and timing of ART initiation

Presenting CD4 cell count	Timing of ART initiation
< 350 cells/uL	This group of women must be started on ART as soon as possible. ART should be started even in the first trimester in women presenting with opportunistic infections or WHO clinical stages 3 and 4.
> 350 cells/uL	These women will need ART primarily for PMTCT. In this scenario, commencement of ART may be delayed until week 14 of pregnancy.

It is well proven that ART prolongs life expectancy of HIV patients and significantly reduces serious AIDS and non-AIDS events. Therefore, ART in pregnant women should be continued for life after delivery regardless of their presenting CD4.

Women should be counselled on the benefits of continuing ART after delivery and the importance of ART adherence. A decision to discontinue ART after delivery can only be considered if the woman is not motivated to be on lifelong ART and her CD4 > 350 cells/uL. To avoid resistance mutation, please refer to Chapter 5 for ways to cease NNRTI based regimes.

7.3 Women who are stable on ART before pregnancy

In general the existing ART 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.

7.4 Choice of agents used for PMTCT

ART used during pregnancy must consist of 2 NRTIs plus either a NNRTI or a boosted PI. The choice of agents is listed in the following table.

Table 7.1 Choice of ART combinations

Preferred	Alternative
TDF + FTC + EFV [a]	*AZT + 3TC + EFV* [a] *AZT + 3TC + NVP* [b] *TDF + FTC + NVP* [b] *TDF + FTC + LPV/RTV* *TDF + FTC + RAL* [c]

a. In the past EFV 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[4].

b. NVP should be used with caution in women with CD4 > 250 cells/uL because of possible increased risk of hepatotoxicity and rash[5].

c. Consider Raltegravir based ART in late presenting women (>28 weeks) with unknown or high viral load (e.g. >100,000 copies/ml). Raltegravir can be switched to EFV or NVP after delivery.

7.5 Mode of delivery

Pre-labor Elective Caesarean Section (PLCS) has been proven to further reduce the risk of transmission[6,7]. The decision between performing PLCS or allowing spontaneous vaginal delivery (SVD) is based largely on the viral load at 32-36 weeks of gestation and whether the mother has received any ARVs in the pre-pregnancy or antenatal period. PLCS should be undertaken at between 38 and 39 weeks' gestation.

Women who have received ART before pregnancy or antenatally and have achieved maximal viral load suppression, have a choice between PLCS or SVD. There is no additional advantage of PLCS over SVD in terms of reduction of transmission in this group[8].

Table 7.2 choice between PLCS or SVD

Viral load at 32-36 weeks	**Mode of delivery**
< 50 copies/ml	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.

7.6 Intrapartum IV Zidovudine infusion

Intrapartum IV Zidovudine infusion (2mg/kg for the 1st hour followed by 1mg/kg/h subsequently) is recommended for women with a viral load of > 1000 copies/mL who present in labour or with ruptured membranes or who are admitted for planned PLCS. Current evidence suggests that intrapartum IV AZT has no additional benefit in prevention of vertical transmission in pregnant women on ART with viral load ≤ 1000 copies/ml during late pregnancy and near delivery[9].

7.7 Women presenting in labour with no prior ART exposure

For the woman who is diagnosed with HIV infection in labour and has not received prior ARVs, start IV AZT infusion immediately.

ART should be commenced immediately with fixed-dose AZT and 3TC and with Raltegravir as the preferred 3rdagent because it also rapidly crosses the placenta. If Raltegravir is not available, NVP or EFV should be used, in order of preference. After delivery, the ART can be switched to recommended first line ART regimen for non-pregnant patients.

The Paediatrician caring for the newborn must be notified to ensure appropriate post exposure ARV prophylaxis for the infant[10, 11]. The HIV exposed infant should receive 6 weeks of oral AZT and 3 doses of NVP at birth, 48 hours later and 96 hours after the 2nd dose.

7.8 Women presenting with spontaneous rupture of membrane (ROM)

The decision for the mode of delivery has to take into account of the maternal viral load, duration of ROM and the expected time of delivery. After ROM there is an increased risk of perinatal HIV transmission of 2% per hour[7]. Chorioamnionitis, a potential complication of prolonged ROM has also been associated with perinatal transmission of HIV[12]. Therefore, delivery should be expedited for women with pre-labour ROM at term, either with induction of labour or Caesarean section. There should be a low threshold to start antibiotics if signs suggestive of chorioamnionitis are present.

If the maternal HIV viral load is <50 copies/mL, vaginal delivery should be attempted unless there is obstetric contraindication. Caesarean section is recommended for women with viral load ≥ 50 copies/mL or unknown viral load.

When premature rupture of membrane (PPROM) occurs at < 34 weeks, intramuscular steroids should be administered in accordance to national guidelines. There should be multidisciplinary discussion between Obstetrician, Paediatrician and ID Physician about the timing and mode of delivery after PPROM.

7.9 Breast-feeding

Breast-feeding is not recommended as it is associated with risk of transmission up to 14%[10]. For women on ART compliance must be stressed if they insist on breast-feeding their baby.

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Chapter 8 Adverse Events of ARVs

Adverse events (AEs) occur with all antiretroviral agents and are 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 13]
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'

Table 8.0 Individual NRTI Drug Substitutions for Toxicity and Intolerance

ARV drugs	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
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 • History of osteomalacia	•Substitute with ZDV / ABC

	• Decrease in bone Mineral density • Hepatic flares	and mineral density fracture • At risk of osteoporosis/ Bone loss • When TDF withdrawn or HBV resistance develops	•Use alternative drug for Hep. B (e.g. entecavir)
ZDA	• Anaemia,neutropaenia • Myopathy • Lipodystrophy (rare)	• Baseline anaemia/ neutropaenia • CD4 count ≤ 200 cells/mm3	•Substitute with TDF / ABC
EFV	• Hallucinations, • psychosis • Depression • Suicidal ideation .	• History of psychiatric illness • Concomitant use of substance with Neuropsychiatric effects • Genetic factor resulting in high serum EFV concentration • Increased absorption with food.	•Substitute with NVP
NVP	• Hepatitis • Severe skin rash (SJS)	• Females with baseline CD4 >250 cells /mm_3 • Males with baseline CD4>400cells / mm3	•Substitute with EFV /PI based regime

Table 8.1 Adverse Events of Antiretroviral Drugs

Bone marrow suppression		
Associated ARV drug	**Comments**	**Management**
ZDV	• Incidence: (anemia) adult 1%, pediatric23%; (leukopenia) 39% • Avoid concurrent bone marrow suppressants • Monitor FBC with differential at weeks–4, 8, 12 (more frequently	• Discontinue ZDV if Hb has dropped≥ 25% of baseline / <8.0 g/dL OR • when patient develops symptomatic anemia and / or leucopenia

	inpatients at risk)	
Central Nervous System Effects		
Associated ARV drug	**Comments**	**Management**
EFV	• Incidence: 40%; only 3% severe enough to justify discontinuation of EFV. • Symptoms include: a. Vivid / abnormal dreams b. Feeling off balance c. Feels like falling over d. Feels like the room is spinning e. Unsteady walk f. Feels like body is spinning g. Feels light-headed h. 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	• 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.

	test	
Gastrointestinal Intolerance		
Associated ARV	**Comments**	**Management**
All ARVs, Especially : Protease inhibitors (PIs): LPV/r ZDV EFV TDF	Symptoms include: abdominal discomfort, loss of appetite, nausea, vomiting, heart burn, abdominal pain, constipation. • Nausea is common with ZDV (vomiting, 6-25%), more than other NRTIs. Occurs in 2-12% of EFV usage. • Diarrhea is frequently seen with ZDV (17%), TDF (16%) 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 cause	•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 drugs if persistent vomiting <u>Diarrhea:</u> • Antimotility agents (e.g., loperamide, diphenoxylate/ atropine) • Monitor pancreatic enzymes <u>Severe GI symptoms:</u> Rehydration and electrolyte replacement as indicated
Hepatotoxicity		
Associated ARVs	**Comments**	**Management**
All NNRTIs **all PIs** **most NRTIs**	<u>NNRTI</u> • 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-naive 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) <u>NRTI</u> Usually occurs after more than 6 months of therapy – ZDV (grade 3 / 4: 2-16%) Risk of hepatotoxicity associated with lactic acidosis with	<u>Symptomatic patients:</u> • Discontinue all ARVs and other potential hepatotoxic agents <u>Asymptomatic patients:</u> • If ALT >5–10x ULN, to consider discontinuing ARVs • After serum transaminases return To normal, start a new ART regimen without the potential offending agent

	microvesicular or macrovesicular hepatic steatosis because of mitochondrial toxicity. <u>Protease inhibitors</u> Usually occurs after weeks to months of Treatment. Indirect hyperbilirubinemia may occur with ATV (35-49%) usage	
Hyperlipidemia		
Associated ARV	**Comments**	**Management**
All PIs (except unboosted ATV) EFV > NVP	<u>NNRTIs</u> • EFV is associated with ↑TG, HDL, LDL (TC ↑by 20-40%). • Increase in TG, TC and LDL less than with PIs <u>NRTIs</u> •ZDV > ABC - TG and LDL ↑ <u>PIs</u> • Cause ↑in LDL, HDL and TG • TG ↑: LPV/r (3-36%) > DRV/r, ATV/r • Usually within 2-3 months of starting PIs.	• 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 16: Drug Interactions for interactions between ARV and lipid-lowering agents*
Hypersensitivity Reaction (HSR)		
Associated ARVs	**Comments**	**Management**
ABC	•Incidence: Up to 8% •Median onset is 9 days; approximately 90% of reactions occur within the first 6 weeks <u>Symptoms include:</u> • (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.	<u>Discontinue ABC and switch to another NRTI</u> • 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 48hrs after discontinuation of ABC <u>More severe cases:</u> • 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.
Lactate : Hyperlactatemia / Lactic Acidosis		
Associated ARVs	**Comments**	**Management**
ZDV >other NRTIs	<u>3 clinical syndromes :</u> a) lactic acidosis with hepatic steatosis b) symptomatic lactatemia without acidosis / liver failure c) asymptomatic lactatemia <u>Symptoms include:</u> • 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 treatment *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*	Lactate 2-5 mmol/L but asymptomatic: Observe. *Note. Do not measure lactate unless symptomatic* Lactate 2-5mmol/L plus symptoms of 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**
ZDV> other	•Fat wasting (lipoatrophy): face,	•Switch from thymidine analogs to

NRTIs	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, PIs and RAL containing regimes, but no causal link has yet been established.	TDF or ABC, which may slow or halt progression but may not fully reverse effects •Surgical options provide cosmetic improvement: •Lipoatrophy: Facial filling with collagen, synthetic polymers or silicone •Lipodystrophy: Liposuction
Nephrotoxicity / Urolithiasis		
Associated ARV Drug	**Comments**	**Management**
TDF ATV	<u>TDF</u> •Symptoms include: ↑serum creatinine, proteinuria, hypophosphatemia, urinary phosphate wasting, glycosuria, hypokalemia, normal anion gap metabolic acidosis •Concurrent use with PI: ↑risk <u>ATV</u> •May cause kidney stone/ crystal formation	<u>Prevention</u> •Drink at least 1.5 - 2 liters of non Caffeinated fluid per day (preferably water) <u>Treatment</u> •Switch to alternative agent •Refer to Urologists when indicated
Neuromuscular Weakness Syndrome (ascending)		
Associated ARV drug	**Comments**	**Management**
NRTIs	It occurs after months of ARV use. <u>Symptoms:</u> Very rapidly progressive ascending demyelinating polyneuropathy, may mimic Guillain-Barre 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 ARV drug	**Comments**	**Management**

ddi + TDF	•ddI with d4T or TDF : ↑frequency •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
Rash		
Associated ARVs	**comment**	**management**
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 mild to moderate rash without constitutional symptoms or biochemical hepatitis, the lead-in (200mg od) dose may be continued without dose escalation until rash resolution, but no longer than 28 days total. •However, the drug should be permanently discontinued if constitutional symptoms are present, the rash is severe or hepatitis is present. Also see Stopping / Interrupting NNRTI. If NVP is interrupted for > 7days, reintroduce with 200mg/day lead-in.
Stevens-Johnson Syndrome (SJS) / Toxic Epidermal Necrosis (TEN)		
Associated ARV drug	**Comments**	**Management**
NVP>EFV Others : ABC , AZT, 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 8.2 ARV drugs and Common Adverse Events

NRTI	
Drug	**Adverse Events**
ABC	Refer to table 14
3TC	• Minimal toxicity • Severe acute hepatitis flare may occur in HBV co-infected patients who discontinue 3TC.

TDF	• Asthenia, headache, diarrhea, nausea, vomiting, and flatulence • Renal insufficiency , Fanconi syndrome (Renal tubular damage reported, risk of serious renal damage is 0.5%) • Osteomalacia • Potential for decrease in bone mineral density • Severe acute hepatitis flare may occur in HBV co-infected patients who discontinue TDF
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)
NNRT	
Drugs	**Adverse events**
EFV	• Rash • Central nervous system symptoms • Increased transaminase levels • Painful gynecomastia • False-positive results reported with some cannabinoid and benzodiazepine screening assays
NVP	• Rash, including Stevens-Johnson syndrome • Symptomatic hepatitis, including fatal hepatic necrosis, has been reported
Protease inhibitor	
Medications	**Common Adverse Events**
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
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
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
Integrase Inhibitors	
RAL	• Increased CK; muscle weakness and rhabdomyolysis • Rash (uncommon)

Chapter 9 Common ARV-Drug Interactions

Table 9.0 Drug Interactions between NRTIs and Other Drugs

Concomitant Drug Class	NRTI	Effect on NNRTI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Antiviral			
Ganciclovir Valganciclovir	ZDV	No significant effect	Potential increase in hematologic toxicities
	TDF	No data.	Serum concentrations of these drugs and/or TDF may be increased. Monitor for dose-related toxicities
Ribavirin	ddI	↑ intracellular ddI	Contraindicated. Do not coadminister. Fatal hepatic failure and other ddI-related toxicities have been reported with coadministration
	ZDV	Ribavirin inhibits phosphorylation of ZDV.	Avoid coadministration if possible, or closely monitor HIV virologic response and possible hematologic toxicities.
Others			
Allopurinol	ddI	ddI AUC ↑ 113% In patients with renal impairment: • ddI AUC ↑ 312%	Contraindicated. Potential for increased ddI-associated toxicities.
	ZDV	ZDV AUC ↑ 31%	Monitor for ZDV-related adverse effects

Table 9.1 Drug Interactions between NNRTIs and Other Drug

Concomitant Drug Class	NNRTI	Effect on NNRTI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Anticoagulants/Antiplatelets			
Warfarin	EFV, NVP	↑ or ↓ warfarin possible	Monitor INR and adjust warfarin dose accordingly
Anticonvulsants			
Carbamazepine Phenobarbital Phenytoin	EFV	Carbamazepine plus EFV: • Carbamazepine AUC ↓ 27% • EFV AUC ↓ 36% Phenytoin plus EFV: • ↓ EFV • ↓ phenytoin possible	Monitor anticonvulsant and EFV levels or, if possible, use alternative anticonvulsant to those listed.
	RPV	↓ RPV possible	Contraindicated. Do not coadminister. Consider alternative anticonvulsant.
	NVP	↓ anticonvulsant and NVP possible	Monitor anticonvulsant and NVP levels and virologic responses or consider alternative anticonvulsant.
Antidepressants			
Bupropion	EFV	Bupropion AUC ↓ 55%	Titrate bupropion dose based on clinical response
Paroxetine	EFV	No significant effect	No dosage adjustment necessary
Sertraline	EFV	Sertraline AUC ↓ 39%	Titrate sertraline dose based on clinical response.
Antifungals			
Fluconazole	EFV	No significant effect	No dosage adjustment necessary
	NVP	NVP AUC ↑ 110%.	Increased risk of hepatotoxicity possible with this combination. Monitor NVP toxicity or use alternative ARV agent
	RPV	↑ RPV possible No dosage adjustment	Clinically monitor for breakthrough fungal

		necessary.	infection.
Itraconazole	EFV	Itraconazole AUC, Cmax, and Cmin ↓ 35% to 44	% Failure to achieve therapeutic itraconazole concentrations has been reported. Avoid this combination if possible. If coadministered, closely monitor itraconazole concentration and adjust dose accordingly
	RPV	↓ itraconazole possible ↑ RPV possible	No dosage adjustment necessary. Clinically monitor for breakthrough fungal infection.
	NVP	↓ itraconazole possible ↑ NVP possible	Avoid combination if possible. If coadministered, monitor itraconazole concentration and adjust dose accordingly
Posaconazole	EFV	Posaconazole AUC ↓ 50%	Avoid concomitant use unless the benefit outweighs the risk. If coadministered, monitor posaconazole concentration and adjust dose accordingly
	RPV	↓ posaconazole possible ↑ RPV possible	No dosage adjustment necessary. Clinically monitor for breakthrough fungal infection.
Voriconazole	EFV	Voriconazole AUC ↓ 77% EFV AUC ↑ 44%	Contraindicated at standard doses. Dose adjustment: Voriconazole 400 mg BID, EFV 300 mg daily
	RPV	↓ voriconazole possible	No dosage

		↑ RPV possible	adjustment necessary. Clinically monitor for breakthrough fungal infection.
	NVP	↓ voriconazole possible ↑ NVP possible	Monitor for toxicity and antifungal response and/or voriconazole level.
Antimalarials			
Artemether/ Lumefantrine		Artemether AUC ↓ 79% Lumefantrine AUC ↓ 56%	Consider alternative ARV or antimalarial drug. If used in combination, monitor closely for antimalarial efficacy and malaria recurrence.
		Artemether AUC ↓ 67% to 72% DHA: • Study results are conflicting. AUC ↓ 37% in one study, no difference in another. Lumefantrine: • Study results are conflicting. Lumefantrine AUC ↓ 25% to 58% in 2 studies but ↑ 56% in another.	Clinical significance unknown. If used, monitor closely for antimalarial efficacy and lumefantrine toxicity
Antimycobacterials			
Clarithromycin	EFV	Clarithromycin AUC ↓ 39%	Monitor for effectiveness or consider alternative agent, such as azithromycin, for MAC prophylaxis and treatment.
	NVP	Clarithromycin AUC ↓ 31.	% Monitor for effectiveness or use alternative agent, such as azithromycin, for MAC prophylaxis and treatment
	RPV	↑ RPV possible	Consider alternative macrolide, such as azithromycin, for MAC prophylaxis and treatment.
Rifabutin	EFV	Rifabutin ↓ 38%	Dose: • Rifabutin

			450–600 mg/day; or • Rifabutin 600 mg 3 times/week if EFV is not coadministered with a PI.
	NVP	Rifabutin AUC ↑ 17% and metabolite AUC ↑ 24% NVP Cmin ↓ 16%	No dosage adjustment necessary. Use with caution.
	RPV	Rifabutin plus RPV 50 mg once daily compared to RPV 25 mg once daily alone: ↔ RPV AUC, Cmin	Increase RPV dose to 50 mg once daily
Rifampin	EFV	EFV AUC ↓ 26%	Maintain EFV dose at 600 mg once daily and monitor for virologic response. Consider therapeutic drug monitoring.
	NVP	NVP ↓ 20% to 58%	Do not coadminister.
	RPV	RPV AUC ↓ 80%	Contraindicated. Do not coadminister.
Benzodiazepines			
Alprazolam	EFV, ETR, NVP, RPV	No data	Monitor for therapeutic effectiveness of alprazolam.
Lorazepam	EFV	Lorazepam Cmax ↑ 16%, AUC ←→	No dosage adjustment necessary.
Midazolam	EFV	Significant ↑ midazolam expected.	Do not coadminister with oral midazolam. Parenteral midazolam can be used with caution as a single dose and can be given in a monitored situation for procedural sedation
Cardiac Medications			
Dihydropyridine CCBs	EFV, NVP	↓ CCBs possible	Titrate CCB dose based on clinical response.
Diltiazem Verapamil	EFV	Diltiazem AUC ↓ 69% ↓ verapamil possible	Titrate diltiazem or verapamil dose based on clinical response
	NVP	↓ diltiazem or verapamil possible	

Corticosteroids			
Dexamethasone	EFV, NVP	↓ EFV, NVP possible	Consider alternative corticosteroid for long-term use. If dexamethasone is used with NNRTI, monitor virologic response.
	RPV	Significant ↓ RPV possible	Contraindicated with more than a single dose of dexamethasone
Hormonal Contraceptives			
	EFV	Ethinyl estradiol ↔ Levonorgestrel (oral) AUC ↓ 64% Norelgestromin AUC ↓ 64% Etonogestrel (implant) AUC ↓ 63% Levonorgestrel (implant) AUC ↓ 48%	Use alternative or additional contraceptive methods. Norelgestromin and levonorgestrel are active metabolites of norgestimate. Unintended pregnancies were observed in women who used EFV and levonorgestrel implant concomitant
	NVP	Ethinyl estradiol AUC ↓ 29%, Cmin ↓ 58% Norethindrone AUC ↓ 18% Etonogestrel (metabolite of oral desogestrel) ↓ 22% Levonorgestrel implant: AUC ↑ 30% N	Consider alternative or additional contraceptive methods No dosage adjustment necessary
	RPV	Ethinyl estradiol: no significant change Norethindrone: no significant change	No dosage adjustment necessary
HMG-CoA Reductase Inhibitors			
Atorvastatin	EFV	Atorvastatin AUC ↓ 32% to 43%	Adjust atorvastatin according to lipid responses, not to exceed the maximum recommended dose.
	RPV	Atorvastatin AUC ←→ Atorvastatinmetabolites	No dosage adjustment

		↑	necessary.
Simvastatin	EFV	Simvastatin AUC ↓ 68%	Adjust simvastatin dose according to lipid responses, not to exceed the maximum recommended dose. If EFV is used with a PI/r, simvastatin and lovastatin should be avoided.
	NVP	↓ lovastatin possible ↓ simvastatin possible	Adjust lovastatin or simvastatin dose according to lipid responses, not to exceed the maximum recommended dose. If ETR or NVP is used with a PI/r, simvastatin and lovastatin should be avoided.
Pravastatin Rosuvastatin	EFV	Pravastatin AUC ↓ 44% Rosuvastatin: no data	Adjust statin dose according to lipid responses, not to exceed the maximum recommended dose.
PDE5 Inhibitors			
Sildenafil	RPV	←→ sildenafil	No dosage adjustment necessary

Table 9.2 Common PI Drug Interactions and Suggested Management

Concomitant Drug	**Protease Inhibitor (PI)**	**Description of Interaction**	**Suggested Management**
Acid reducer			
Antacids	ATV/r	↑pH →↓ATV solubility; ↓ ATV AUC & absorption[3]	Give ATV at least 2 hours before or 1 to 2 hours after antacids or buffered medications.
H2 Receptor Antagonists	ATV/r	↑pH ↓ATV solubility; ATV AUC ↓48% when ATV/r was administered 1hr after a single dose of ranitidine 150mg in a	H2-receptor antagonist can be administered with ATV/r but dose should not exceed a dose equivalent to

		study of 12 healthy volunteers[1]	famotidine 40mgBID in treatment naive 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*
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 unavoidable, PPIs should not exceed dose equivalent of omeprazole 20mg OD and should be administered 12hrs apart from ATV/r.
Antifungal			
Fluconazole	◊ All PIs (except tiprinavir)	No significant effect [3,7,8,9,10]	No dose adjustment necessary [3,7,8,9,10]
Itraconazole	ATV/r, DRV/r, LPV/r	Potential for bidirectional inhibition between itraconazole and PIs [3,7,8,9,10]	Do not exceed itraconazole200mg/day. Use with caution and monitor for toxicities. [3,7,8,9,10]
Ketoconazole	ATV/r, DRV/r, LPV/r	Potential for bidirectional inhibition between ketoconazole 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]
posaconazole	ATV/r ATV DRV/r	ATV AUC ↑ 146% ATV AUC ↑ 268% ↑ PI possible	Monitor for adverse effects of ATV. If coadministered,

	LPV/r	↑ posaconazole possible	consider monitoring posaconazole concentrations. Monitor for PI adverse effects.
Voriconazole	ATV/r, DRV/r, 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]
Antibiotics			
Clarithromycin	ATV (unboosted)	clarithromycin AUC ↑ 94%	May cause QTc prolongation. Reduce clarithromycin dose by 50%. Consider alternative therapy (eg, azithromycin).
	All PI/r,	↑ clarithromycin expected	Consider alternative macrolide (eg, azithromycin)
	ATV/r	DRV/r ↑ clarithromycin AUC 57% FPV/r ↑ clarithromycin possible LPV/r ↑ clarithromycin expected RTV 500 mg BID ↑ clarithromycin 77% SQV unboosted ↑ clarithromycin 45% TPV/r ↑ clarithromycin 19% clarithromycin ↑ unboosted SQV 177% clarithromycin ↑ TPV 66%	Monitor for clarithromycin-related toxicities or consider alternative macrolide (eg, azithromycin). Reduce clarithromycin dose by 50% in patients with CrCl 30–60 mL/min. Reduce clarithromycin dose by 75% in patients with CrCl <30 mL/min.
Erythromycin	DRV/r, LPV/r,	Erythromycin concentrations may increase but no data on the extent of interaction. [7,8,9,1]	Careful monitoring of therapeutic and adverse effects is recommended. [7,8,9,10]
Rifampicin	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]

Antimalarials			
Artemether/ Lumefantrine	DRV/r	artemether AUC ↓ 16% DHAa AUC ↓ 18% lumefantrine AUC ↑ 2.5-fold	Clinical significance unknown. If used, monitor closely for antimalarial efficacy and lumefantrine toxicity.
	LPV/r	artemether AUC ↓ 40% DHA AUC ↓ 17% lumefantrine AUC ↑ 470%	
Artesunate/ Mefloquine	LPV/r	dihydroartemisinin AUC ↓ 49% mefloquine AUC ↓ 28% LPV ↔	Clinical significance unknown. If used, monitor closely for antimalarial efficacy
Atovaquone/ Proguanil	ATV/r LPV/r	ATV/r ↓ atovaquone AUC 46% and ↓ proguanil AUC 41% LPV/r ↓ atovaquone AUC 74% and ↓ proguanil AUC 38%	No dosage recommendation. Consider alternative drug for malaria prophylaxis, if possible
Mefloquine	RTV	With RTV 200 mg BID: RTV AUC ↓ 31%, Cmin ↓ 43%; n● mefloquine	Use with caution. Effect on exposure of RTV-boosted PIs is unknown.
Anticonvulsants			
Carbamazepine (CBZ)	ATV/r, LPV/r	Co-administration 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]
	DRV/r	CBZ AUC ↑45%. No significant effect on DRV exposure.[7]	Monitor anticonvulsant level and adjust dose accordingly. [7]
Lamotrigine (LTG)	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]
Phenytoin (PHT) / Phenobarbitone (PHB)	ATV/r, DRV/r, 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)	ATV/r, DRV/r, LPV/r	Possible decrease in VPA level by ritonavir (induces	Monitor anticonvulsant level and adjust dose accordingly. [3,7,8,10,16]

		glucoronidation) but no significant effect on PIs. [3,7,8,10,16]	
Benzodiazepines			
Alprazolam Clonazepam Diazepam	All PIs	↑ benzodiazepine possible RTV (200 mg BID for 2 days) ↑ alprazolam half-life 222% and AUC 248%	Consider alternative benzodiazepines such as lorazepam, oxazepam, or temazepam.
Lorazepam	All PIs	No data	These benzodiazepines are metabolized via non-CYP450 pathways; thus, there is less interaction potential than with other benzodiazepines
Midazolam	All PIs	↑ midazolam expected	Do not coadminister oral midazolam and PIs. Parenteral midazolam can be used with caution when given as a single dose in a monitored situation for procedural sedation
			Monitor clinical effect and withdrawal symptoms.
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 obtain at least 35mcg of ethinylestradiol.[19]
	Δ DRV/r, Δ LPV/r	Ethinyl estradiol AUC↓44-55%[20,21]No clinically significantinteractions.[8,9]	Use alternative or additional method [7,9]
HMG-CoA Reductase Inhibitors			
Atorvastatin	ATV, ATV/r DRV/r	↑ atorvastatin possible	Titrate atorvastatin dose carefully and use lowest dose necessary.
Pravastatin	ATV/r	No data	Use lowest starting dose of pravastatin and

			monitor for efficacy and adverse effects.
	DRV/r	With DRV/r, pravastatin AUC • ↑ 81% following single dose of pravastatin • ↑ 23% at steady state	Use lowest possible starting dose of pravastatin with careful monitoring
	LPV/r	pravastatin AUC ↑ 33%	No dose adjustment necessary
Rosuvastatin	ATV/r, LPV/r	ATV/r ↑ rosuvastatin AUC 3-fold and Cmax ↑7-fold LPV/r ↑ rosuvastatin AUC 108% and Cmax ↑ 366%	Titrate rosuvastatin dose carefully and use the lowest necessary dose. Do not exceed 10 mg rosuvastatin daily.
	DRV/r	rosuvastatin AUC ↑ 48% and Cmax ↑ 139%	Titrate rosuvastatin dose carefully and use the lowest necessary dose while monitoring for toxicities
Simvastatin	All PIs	Significant ↑ simvastatin level: SQV/r 400 mg/400 mg BID ↑ simvastatin AUC 3059%	Contraindicated. Do not coadminister.
Cortocosteroids			
Budesonide Fluticasone, Mometasone Systemic/Inhaled	All PIs	↓ PI levels possible ↑ glucocorticoids	Coadministration can result in adrenal insufficiency and Cushing's syndrome. Do not coadminister unless potential benefits of systemic budesonide outweigh the risks of systemic corticosteroid adverse effects
Dexamethasone Systemic	All PIs	↓ PI levels possible	Use systemic dexamethasone with caution. Consider alternative corticosteroid for long-term use.
Prednisone	All PIs	↑ prednisolone poss	Use with caution. Coadministration can result in adrenal insufficiency and Cushing's syndrome. Do not coadminister unless

			potential benefits of prednisone outweigh the risks of systemic corticosteroid adverse effects.
Cardiac Medications			
Antiarrhythmics	All PIs	↑ antiarrhythmic possible	Use with caution.
Amiodarone	All PIs	↑both amiodarone and PI possible	Use with caution. Monitor for amiodarone toxicity and consider ECG and amiodarone drug level monitoring.
Beta-blockers	All PIs	↑ beta-blockers possible	May need to decrease beta-blocker dose; adjust dose based on clinical response. Consider using beta-blockers that are not metabolized by CYP450 enzymes (eg, atenolol, labetalol, nadolol, sotalol)
Calcium Channel Blockers (CCBs) (except diltiazem)	All PIs	↑ dihydropyridine possible ↑ verapamil possible	Use with caution. Titrate CCB dose and monitor closely.
Digoxin	All PIs	RTV (200 mg BID) ↑ digoxin AUC 29% and ↑ half-life 43%	Use with caution. Monitor digoxin levels. Digoxin dose may need to be decreased. Titrate initial digoxin dose.
Diltiazem	ATV/r, ATV	Unboosted ATV ↑ diltiazem AUC 125% Greater ↑ likely with ATV/c or ATV/r	Decrease diltiazem dose by 50%. ECG monitoring is recommended.
	DRV/r, LPV/r	↑ diltiazem possible	Use with caution. Adjust diltiazem according to clinical response and toxicities.
Antidepressants, Anxiolytics, and Antipsychotics			
Fluvoxamine	All PIs	↑ or ↓ PI possible	Consider alternative therapeutic agent.
Other Selective Serotonin Reuptake Inhibitors (SSRIs) (eg, citalopram,	RTV DRV/r	Esitalopram ←→ paroxetine AUC ↓ 39% sertraline AUC ↓ 49%	Titrate SSRI dose based on clinical response

escitalopram, fluoxetine, paroxetine, sertraline)	ATZ/r,LPV/r	No data	
Quetiapine	All PIs	↑ quetiapine expected	Starting quetiapine in a patient receiving a PI: • Start quetiapine at the lowest dose and titrate up as needed. Monitor for quetiapine effectiveness and adverse effects. Starting a PI in a patient receiving a stable dose of quetiapine: • Reduce quetiapine dose to 1/6 of the original dose. Closely monitor for quetiapine effectiveness and adverse effects.
Other Antipsychotics (eg, perphenazine, risperidone)	All PIs	↑ antipsychotic possible	Titrate antipsychotic dose using the lowest initial dose, or adjust maintenance dose accordingly. Monitor for toxicities.
Tricyclic Antidepressants Amitriptyline, Desipramine, Doxepin, Imipramine, Nortriptyline	All PIs	↑ TCA expected	Use lowest possible TCA dose and titrate based on clinical assessment and/or drug levels.
Anticoagulants and Antiplatelets			
Apixaban	All PIs	↑ apixaban expected	Avoid concomitant use
Dabigatran	All PIs	↑ dabigatran possible	
Rivaroxaban	All PIs	↑ rivaroxaban	
Ticagrelor	All PIs	↑ ticagrelor expected	
Warfarin	All PIs	↓ warfarin possible	Monitor INR closely when stopping or starting PI/r and adjust warfarin dose accordingly.
Immunosuppressants			
Cyclosporine, Everolimus,	All PIs	↑ immunosuppressant expected	Initiate with an adjusted dose of

Sirolimus, Tacrolimus			immunosuppressant to account for potential increased concentrations of the immunosuppressant and monitor for toxicities. Therapeutic drug monitoring of immunosuppressant is recommended. Consult with specialist as necessary.
Miscellaneous Drugs			
Salmeterol	All PIs	↑ salmeterol possible	Do not coadminister because of potential increased risk of salmeterol-associated cardiovascular events.
Colchicine	All PIs	significant ↑ colchicine expected	For Treatment of Gout Flares: • Colchicine 0.6 mg x 1 dose, followed by 0.3 mg 1 hour later. Do not repeat dose for at least 3 days. For Prophylaxis of Gout Flares: • Colchicine 0.3 mg once daily or every other day For Treatment of Familial Mediterranean Fever: • Do not exceed colchicine 0.6 mg once daily or 0.3 mg BID. Do not coadminister in patients with hepatic or renal impairment

Table 9.3 Common NRTIs Interactions and Suggested Management

Concomitant Drug Class	Integrase inhibitor	Effect on NNRTI and/or	Dosing Recommendations

		Concomitant Drug Concentrations	and Clinical Comments
Aluminium, Magnesium +/- Calcium-Containing Antacids	RAL	Al-Mg Hydroxide Antacid: • RAL Cmin ↓ 54% to 63% CaCO3 Antacid: • RAL Cmin ↓ 32%	Do not coadminister RAL and AlMg hydroxide antacids. Use alternative acid reducing agent. No dosing separation necessary when coadministering RAL and CaCO3 antacids
PPIs	RAL	RAL AUC ↑ 212% and Cmin ↑ 46%	No dosage adjustment necessary
Antidepressants/Anxiolytics/Antipsychotics			
SSRIs Citalopram Escitalopram Fluoxetine Paroxetine Sertraline	RAL	↔ RAL ↔ citalopram	No dosage adjustment necessary
Antimycobacterials			
Rifabutin	RAL	AL AUC ↑ 19% and Cmin ↓ 20%	No dosage adjustment necessary
	RAL	RAL 400 mg: • RAL AUC ↓ 40%, Cmin ↓ 61% Compared with RAL 400 mg BID alone, Rifampin with RAL 800 mg BID: • RAL AUC ↑ 27%, Cmin ↓ 53%	Dose: • RAL 800 mg BID Monitor closely for virologic response or consider using rifabutin as an alternative rifamycin
Hormonal Contraceptives	RAL	No clinically significant effect	No dosage adjustment necessary
Polyvalent Cation Supplements Mg, Al, Fe, Ca, Zn, including multivitamins with minerals	All INSTIs	↓ INSTI possible DTG n when administered	If coadministration is necessary, give INSTI at least 2

		with Ca or Fe supplement simultaneously with food	hours before or at least 6 hours after supplements containing polyvalent cations, including but not limited to the following products: cationcontaining laxatives; Fe, Ca, or Mg supplements; and sucralfate. Monitor for virologic efficacy. DTG and supplements containing Ca or Fe can be taken simultaneously with food. Many oral multivitamins also contain varying amounts of polyvalent cations; the extent and significance of chelation is unknown.

Key to Symbols: ↑ = increase, ↓ = decrease, ↔ = no change

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Chapter 10 Tuberculosis and HIV Co-Infection

Introduction

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

10.1 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.

10.2 Role of ART in HIV individuals with TB

HAART during anti TB treatment reduces mortality and results in earlier sputum smear/ culture conversion. WHO recommends ART in all TB / HIV co infected patients regardless of CD4.

However earlier ART is not associated with reduction in deaths in patients with CD4>50cells/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 co-infection, as early ART treatment is associated with higher mortality.[5]

10.3 Optimal timing of ART in treatment-naïve patients

1) Initiation of HAART is warranted regardless of CD4 count in TB-HIV co-infected patients
2) The optimal timing of integrated HIV and TB therapy depends on pt's immune status

   In patients with Pulmonary TB (smear positive):

   i. CD4 < 50 cells – early ART (within 2 weeks of initiation of TB therapy)
   ii. CD4 50 -250 cells – timing of ART depends on severity of HIV (In presence of low Karnofsky score, low body mass index, low haemoglobin, low albumin, organ system dysfunction or extent of disease, ART should be initiated within 2-4 weeks of TB therapy. If not, to start within 8-12 weeks of TB therapy)
   iii. CD4 > 250 cells – ART can be started during maintenance phase of TB therapy
3) Other clinical considerations of starting ART includes tolerability to TB therapy and ability to swallow multiple pills, risk of IRIS, drug toxicity
4) For TB meningitis, initiation of ART is deferred to maintenance phase (after 2 months of intensive phase) as no mortality benefits with higher adverse events shown in cohorts with early ART initiation

10.4 Immune Reconsitution Inflammatory Syndrome (IRIS)

Risk of IRIS depends baseline CD4 cell and timing of ART in relation to TB therapy

10.5 Choice of ART in combination with rifampicin based anti-TB regime

1) Combination of backbone (2 nucleoside analogs) and base (either a non-nucleoside reverse transcriptase inhibitor, protease inhibitor or integrase strand transfer inhibitor)

- **NRTI**

No significant interaction between nucleoside analogs with rifampicin

- **NNRTI**

I. For patients on rifampicin based antituberculous regime, initiation of efavirenz-based therapy is recommended (reduction of nevirapine concentration with concomitant rifampicin is greater than with efavirenz). The standard dosage of efavirenz of 600mg daily is recommended.
II. Virologically suppressed patient on nevirapine-based therapy who developed TB can continue with the same ART regime.
III. If nevirapine is initiated with rifampicin, it is recommended to start nevirapine 200mg bd from the start. (Initiation of the two-week lead-in phase of once-daily dosing dose of nevirapine is not recommended as it can increase risk of virological failure)

- **PI**

I. Use of rifabutin with protease-based inhibitor is recommended
II. The recommended dosage of rifabutin is reduced to **150mg daily or 300mg 3 times-weekly** (usual dose is 300mg/day). This applies for both with or without ritonavir boosted PI.

- **ISTI**

I. Raltegravir should be used with caution together with rifampicin (reduced raltegravir drug concentration by 40-60%). For use with rifampicin, the recommended dosing of Raltegravir is 800mg bd
II. Standard dosing of Raltegravir (400mg bd) is recommended for use with rifabutin
III. Use of rifabutin does not affect dolutegravir concentration

2) Anti-retroviral medications, including NNRTI and PI, do not have significant drug interaction with other first-line and second-line anti-TB drugs

Introduction of TB therapy in HIV patients already on ART

1. TB therapy should be started as soon as possible in patients who are already on ART

2. If patients already achieved viral load suppression and tolerates ART well, it is preferable to initiate rifampicin-based anti-TB that will not lead to significant interaction that could interfere with viral suppression
    i. In patient taking protease-inhibitor containing ART, the preferred choice would be rifabutin
    ii. In patient taking non-nucleoside reverse transcriptase inhibitor containing ART, rifampicin would be the preferred choice
    iii. In patient taking integrase strand transfer-inhibitor (ISTI), i.e raltegravir containing ART, use of rifabutin is recommended
3. The duration of rifampicin-containing TB treatment in HIV patients should be at least 6 months

10.6 Multi-drug resistant TB and HIV

- ART is recommended for all patients with HIV and drug-resistant TB requiring second-line anti-TB drugs irrespective of CD4 cell count, as early as possible (within the first 8 weeks) following initiation of anti-TB

10.7 Co-Trimaxazole prophylaxis

- Should be given to all HIV-infected patients with active TB disease regardless of CD4 cell count

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Chapter 11: Management of Hepatitis B and HIV co-infection

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

11.1 Effects of HIV on HBV disease progression

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

11.2 Effects of ARVs on HBV

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

Goals of Therapy

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

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

Pre- treatment assessments:

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

11.3 Treatment Recommendations for HBV and HIV co-infection

- Patients with HBV/HIV co-infection should be advised to abstain from alcohol and receive hepatitis A vaccination if the patient is not immune to it.
- It is important to monitor HBV DNA levels in patients with HBV/HIV co-infections. This is because in HBV/HIV co-infected patients, the elevations of transaminase levels do not correlate with the level of HBV replications.
- As it is now recommended to start ART in all HIV infected patients, irrespective of CD4 cell count or WHO clinical stage, all HIV/HBV co-infected individuals will be treated as long as the antiretroviral regime includes two active drugs with anti-HBV action.

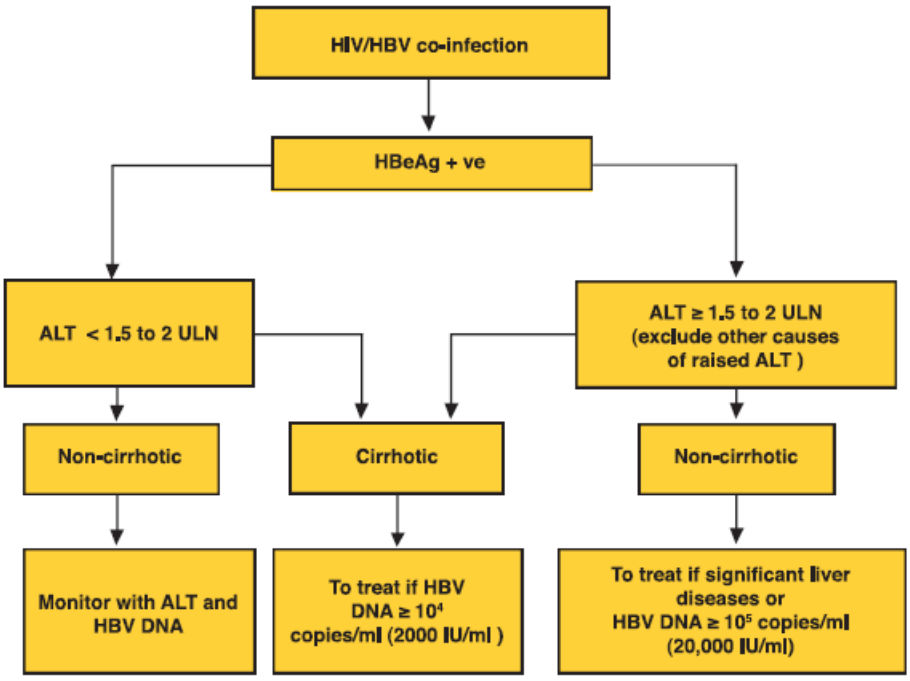
In setting where HAART therapy is initiated based on CD4

- start ART in all HIV/HBV co-infected individuals who require treatment for their HBV

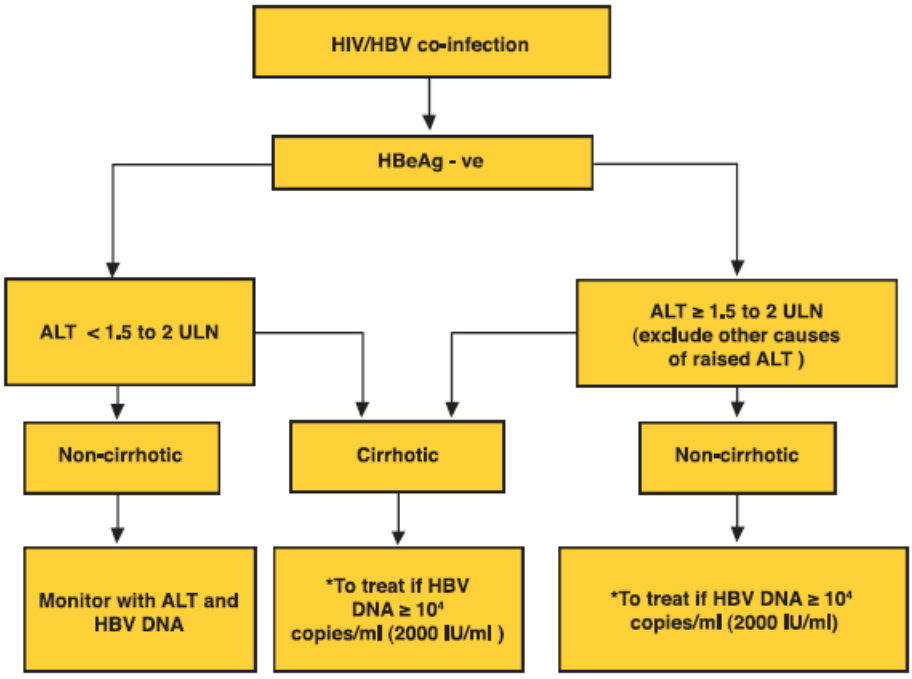
infection, irrespective of CD4 cell count or WHO clinical stage.

- Decision to treat HBV infection depends on ALT, HbeAg status, HBV DNA levels and whether patient has any evidence of liver cirrhosis. Refer algorithm 1 and 2
- Patient whose ALT 2 ULN, HBeAg negative and HBV DNA 104 copies/ml are unlikely to have active viral replication or active liver disease31. Hence, anti-HBV therapy is not recommended.However, ALT and HBV DNA need to be monitored regularly.
- Antiretroviral regime which includes two active drugs with anti-HBV action is the preferred option. The suggested ARVs regime should consist of a combination of Tenofovir and Lamivudine or Emtricitabine as the NRTI backbone[1]
- The duration of treatment for treatment of HBV / HIV co-infection is lifelong.

Algorithmn 1 : HBV treatment if HbeAg+



Algorithmn 2 : HBV treatment if HbeAg-



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

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Chapter 12: HIV and hepatitis c coinfection

12.1 Introduction

Hepatitis C (HCV) affects 5-15% of the 33 million people living with HIV worldwide and up to 90% of injecting drug users [1, 2]. The prevalence of HIV-HCV co-infection among HIV positive patients ranged broadly from 1.2-98.5% in South and Southeast Asia [3].

Liver disease has become a major cause of death in HIV infection and 66% are secondary to HCV[4]. Strategies to prevent, screen and treat HCV in people with HIV are becoming increasingly important.

Treatment with pegylated interferon α (Peg IFN) and ribavarin (RBV) has been the mainstay of treatment for many years. The introduction of direct acting antivirals (DAA) has revolutionized the treatment of HCV[5]. The co-infected population is no longer a special difficult-to-treat population.

12.2 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[6].

12.3 Effects of Antiretrovirals on HCV infection

ART was associated with a decrease rate of liver fibrosis progression (7). These patients are however at greater risk of ART induced hepatotoxicity [8].

Goal of treatment

Cure: Sustained Virological Response (SVR-undetectable HCV RNA 12 or 24 weeks after the end of therapy when treated with DAA or Peg IFN/RBV respectively). This is associated with improved liver histology and decreased risk of progression to cirrhosis, end stage liver disease and hepatocellular carcinoma and death [9].

Candidates considered for HCV treatment

Treating ALL patients with HCV should be the ultimate goal as treatment prevents transmission of hepatitis C and reduces risk of liver related morbidity and mortality. However, due to multiple constraints, only a few have access to treatment.

Consider treatment in these patients:

Motivated patients keen for treatment and likely to stay on treatment and attend regular follow up.
Normal liver or non decompensated liver cirrhosis (Child's grade A cirrhosis).
On stable ART with CD4 count > 200 cells/ml.
No underlying OIs.

When considering Peg IFN and/or RBV therapy:

Patients with psychiatric, ophthalmologic, respiratory, cardiac or neurological illnesses should be on regular treatment and follow up from the respective specialities.
Negative TB workout (CXR, Mantoux +/- sputum).

12.4 Pretreatment assessment

i)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.

ii) Status of liver damage:

Stage fibrosis (Fibro Scan, liver biopsy).

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

Ultrasound of the Hepatobiliary system and alpha-feto protein (if suspect liver cirrhosis or HCC).

iii) Others:

Full blood count, renal profile, ECG.

CD4 count and HIV RNA Viral load.

Additional test when using Peg IFN +/- RBV:

Thyroid function test.

UPT (female patients).

12.5 Treatment Recommendation for HCV/HIV co-infection [10]

i) General:

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 (DDI) and increased risk for drug toxicity.

ii) Antiviral agents:

DAAs are the treatment of choice. The treatment duration and outcome in co-infected patients is comparable to monoinfected patients. There are fewer DDIs between DAAs and ART. However, access to DAAs is still limited due to the high cost of DAAs [11].Therefore, Peg IFN + RBV remains as the first line treatment in Malaysia.

Treatment options [12, 13]**:**

i) Combination of Peg IFN) plus weight based ribavarin.

Duration of therapy may vary from 24 to 48 weeks depending on HCV Genotype and presence or absence of cirrhosis.

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:

Initiating ART should follow the same principles as in HIV monoinfection

Tenofovir + Lamivudine/Emtricitabine + Efavirenz OR

Abacavir + Lamivudine + Efavirenz

Avoid:

Zidovudine: risk of anaemia

ii) Direct acting antiviral (DAA) +/- RBV [14-22]

DAAsregistered in Malaysia includessimeprevir, sofosbuvir, daclatasvir, sofosbuvir/ ledipasvir, 3D (Ombistasvir/ paritaprevir/ritonavir/ dasabuvir).

Duration of treatment ranges from 12-24 weeks depending on presence of liver cirrhosis, genotype and previous hepatitis C treatment experience.
A shorter duration of 8 weeks treatment with of Sofosbuvir/Ledipasvir may be considered for genotype 1, treatment naïve non cirrhotic patients with HCV RNA <6 million copies/ml.

Drug-drug interections (DDIs) to consider when using DAAs:

a) Daclatasvirand ritonavir-boosted regimens (decrease DCV to 30mg od).
b) Daclatasvirand NNRTI regimens, efavirenzand nevirapine(increase DCV to 90 mg od).
c) Ledipasvir increases tenofovir levels. Avoid in those with CrCl below 60 mL/min
d) Ledipasvir should be avoided with combination of TDF with ritonavir-boosted or cobicistat-boosted regimens unless
antiretroviral regimen cannot be changed and high urgency of hepatitis C treatment.
e) 3D should not be used with NNRTI regimens, efavirenzand nevirapine
f) 3D should not be used with lopinavir and ritonavir.

DDIs can be screened through www.hep-druginteractions.org

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Chapter 13 ART among Serodiscordant Couples

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<350cells/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 500cells/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 ART in serodiscordant couple
•To reduce the risk of HIV transmission to the seronegative partner.
•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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Chapter 14 Antiretroviral Therapy for Illicit Drug Users

14.1 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.

14.2 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.

14.2 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 centers. 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 drug toxicities, which threatens ongoing adherence to therapy.3

Table 14.0 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% EC ddI unchanged	Buffered ddI dose increase may be considered or use EC ddI instead
Emtricitabine (FTC)	No data	No data	
Lamivudine (3TC)	None	None	No dose adjustment necessary
Stavudine (d4T)	None	Reduces d4T 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	
	None	None	
Zidovudine (AZT)	None	AZT 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	
Protease Inhibitors (PIs)			
atazanavir (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
Darunavir (DRV)	None	None	
Lopinavir / ritonavir (LPV/r)	None	None	

			methadone dose as clinically indicated.
Integrase Inhibitors			
Raltegravir (RAL)	None	None	No dose adjustment necessary
Others			
Maraviroc (MRV)	No data–potentially safe	No data–potentially safe	

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 ofprolonging 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 14.1 Interactions of Clinical Significance Between Buprenorphine and ART4,5

Antiretroviral Agent	**Effect on Buprenorphine**	**Buprenorphine Effect on Antiretroviral Agent**	**Buprenorphine 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 dose adjustment necessary
Stavudine (d4T)	None	None	—
Tenofovir (TDF)	None	None	No dose adjustment necessary
Zidovudine (AZT)	None	None	No dose 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	Buprenorphine	None	No dose adjustment

TMC-125)	AUC ↓ 25%		necessary
Nevirapine (NVP)	Methadone AUC ↓41%	None	No dose adjustment necessary
Protease Inhibitors (PIs)			
atazanavir (ATV)	Buprenorphine AUC ↑ 93%; norbuprenorphine AUC ↑ 76%	↓ ATV levels possible	If boosted with ritonavir, Methadone AUC ↓16%–18%;
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 dosage adjustment necessary
Lopinavir / ritonavir (LPV/r)	None	None	No dosage adjustment necessary
Ritonavir (RTV)	Potential for increased buprenorphine effects	No data	Observe; buprenorphine dose reduction may be necessary
Integrase Inhibitors			
Raltegravir (RAL)	No data– potentially safe	No data– potentially safe	Observe; buprenorphine dose reduction may be necessary
Others			
Maraviroc (MRV)	No data– potentially safe	No data– potentially safe	No dose adjustment 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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Chapter 15 Postexposure Prophylaxis (PEP) for HIV Infection Following Occupational Exposures

15.1 Introduction

The most common occupational exposure to HIV amongst health care worker (HCW) is needlestick 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.

15.2 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.

15.3 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 (e.g. dermatitis, chapped skin, abrasion or open wound) to blood, visibly bloody fluid or OPIM.

15.4 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 this 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.

Table 15.0 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 Nonintact 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		

15.5 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 (e.g. 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.

15.6 Which ARV drug regime to use?

Table 15.1 ARV drugs 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	<u>Preferred</u> Raltegravir 400mg bd <u>Alternative</u> 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 should be started as soon as possible.
(I.e. Tenofovir + Emtricitabine OR Zidovudine + Lamivudine)

15.7 Timing of Initiation of PEP:

All efforts have 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.

15.8 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.

15.9 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.

Table 15.2 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 AZT)		FBC (if on AZT), 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

Chapter 16: non occupational post exposure prophylaxis (nPEP)

16.1 Introduction

Situations that may prompt request for nPEP include:

1. Unprotected sex
2. Protected sex with condom failure (slippage or breakage)
2. Unsafe needle sharing
3. Episodic exposure of mucus membranes or wounds to blood

Treatment of high-risk exposures should always be combined with education and counselling to prevent future exposures.

16.2 Initial Assessment for nPEP

Patients who present for nPEP should be assessed promptly so that nPEP if required, can be initiated within the appropriate time frame. (See timing of nPEP)

Risk assessment and initiation of nPEP should occur in clinical settings that can provide the following:

1. Assessment of HIV risk following exposure
2. HIV and STI testing and treatment
3. Prevention and risk-reduction counseling
4. Clinicians with expertise in the use of ART
5. Timely access to care and initiation of nPEP

Table 16.0 Estimated per act risk of acquiring human immunodeficiency virus (HIV) from an infected source, by exposure act[a]

Exposure type	Rate of HIV acquisition per 10,000 exposures
Parenteral	
Blood transfusion	9,2 50
Needle sharing during injection drug use	63
Percutaneous (needlestick)	23
Sexual	
Receptive anal intercourse	138
Receptive penile-vaginal intercourse	8
Insertive anal intercourse	11
Insertive penile-vaginal intercourse	4
Receptive oral intercourse	LOW
Insertive oral intercourse	LOW
Other[b]	
biting	negligible
spitting	negligible
Sharing sex toys	negligible

Source: http://www.cdc.gov/hiv/policies/law/risk.html

a. Factors that may increase the risk of HIV transmission include sexually transmitted diseases, acute and late-stage HIV infection, and high viral load. Factors that may decrease the risk include condom use, male circumcision, antiretroviral treatment, and pre-exposure prophylaxis. None of these factors are accounted for in the estimates presented in the table.

b. HIV transmission through these exposure routes is technically possible but unlikely and not well documented.

Immediate management and assessment of an individual with known or suspected exposure to HIV (Box 1)

- Do not douche the vagina or rectum after sexual exposure
- After oral exposure, spit out blood/body fluids and rinse with water
- Wash wounds and skin sites that have been in contact with blood or body fluids
- Do not inject antiseptics or disinfectants into wounds
- Do not milk wounds
- Irrigate mucous membranes or eyes (remove contact lenses) with water or saline

Evaluate exposure. Is nPEP indicated?

A risk-benefit analysis should be undertaken for every individual presenting following an exposure and the decision to initiate nPEP made on a case-by-case basis (Table 22).

If source individual is unknown HIV status, proactive attempts should be made to establish the HIV status of the source as early as possible. [28]

If source individual is known to be HIV-positive, attempts should be made at the earliest opportunity to determine the HIV viral load, resistance profile and treatment history.

nPEP is not routinely recommended after any type of sex with HIV-positive source on antiretroviral therapy (ART) with a **confirmed** and **sustained** (>6 months) undetectable plasma HIV viral load (<200c/ml). [28]

Table 16.1 Assessing the need of nPEP based on exposure

Source HIV status				
	HIV positive		**Unknown HIV status**	
	HIV VL unknown / detectable (>200copies/ml)	HIV VL undetectable (<200copies/ml)	From high prevalence country / risk-group (e.g. MSM) *	From low prevalence country / group
Receptive anal sex	Recommend	Not recommended[%] *Provided source has confirmed HIV VL<200c/ml for >6 months*	Recommend	Not recommended
Insertive anal sex	Recommend	Not recommended	Consider[†]	Not recommended
Receptive vaginal sex	Recommend	Not recommended	Consider[†]	Not recommended
Insertive vaginal sex	Consider[&]	Not recommended	Consider[†]	Not recommended
Fellatio with ejaculation‡	Not recommended	Not recommended	Not recommended	Not recommended
Fellatio without ejaculation‡	Not recommended	Not recommended	Not recommended	Not recommended

Splash of semen into eye	Not recommended	Not recommended	Not recommended	Not recommended
Cunnilingus	Not recommended	Not recommended	Not recommended	Not recommended
Sharing of injecting equipment**	Recommended	Not recommended	Consider	Not recommended
Human bite§	Not recommended	Not recommended	Not recommended	Not recommended
Needle stick from a discarded needle in the community			Not recommended	Not recommended

* High prevalence countries or risk-groups are those where there is a significant likelihood of the source individual being HIV positive. Within the UK at present, this is likely to be MSM, IDUs from high-risk countries (see ** below) and individuals who have immigrated to the UK from areas of high HIV prevalence, particularly sub Saharan Africa (high prevalence is >1%). HIV prevalence Country specific HIV prevalence can be found in UNAIDS Gap Report: http://www.unaids.org/en/resources/campaigns/2014/2014gapreport/gapreport

% The source's viral load must be confirmed with the source's clinic as <200c/ml for >6 months. Where there is Any uncertainty about results or adherence to ART then PEP should be given after unprotected anal intercourse with an HIV positive person

† More detailed knowledge of local prevalence of HIV within communities may change these recommendations from consider to recommended in areas of particularly high HIV prevalence. Co-factors in Box 1 that influence the likelihood of transmission should be considered &Co-factors in Box 1 that influence the likelihood of transmission should be considered ‡ PEP is not recommended for individuals receiving fellatio i.e. inserting their penis into another's oral cavity. For individuals giving fellatio PEP is not recommended unless co-factors 1 & 2 in Box 1 are present e.g HIV seroconversion and oropharyngeal trauma / ulceration, see notes in guideline above **HIV prevalence amongst IDUs varies considerably depending on country of origin and is particularly high in IDUs from Eastern Europe and central Asia. Region-specific estimates can be found in the UNAIDS Gap Report http://www.unaids.org/sites/default/files/media_asset/05_Peoplewhoinjectdrugs.pdf

§ A bite is assumed to constitute breakage of the skin with passage of blood. See notes in guideline above about extreme circumstances where PEP could be considered after discussion with a specialist

Adapted fromBASHH UK guideline for the use of HIV post exposure prophylaxis following sexual exposure (PEPSE) 2015

Factors that increase the risk of HIV transmission include (Box 2)

- Receptive anal intercourse[7-9]
- High plasma viral load (HIV seroconversion or with advanced disease)[10, 11]
- Sexually transmitted infections in the source or exposed individual, especially genital ulcer disease and symptomatic gonococcal infections[12, 13]
- Breach in genital mucosal integrity (eg trauma, genital piercing or genital tract infection)[12,13]
- Breach in the oral mucosal integrity when performing oral sex[12,13]
- Intra-arterial injection with a needle or syringe containing HIV-infected blood[7-9]
- Uncircumcised status of the insertive HIV negative partner practicing IAI or IVI[11,14,15]
- Cervical ectopy[11,14,15]
- Menstruation[11,15]
- Ejaculation[11]

Flow chart for initiation of nPEP:

STEP 1: If nPEP recommended or considered

↓

STEP 2: Is patient presenting within 72 hours?

↓

STEP 3: Initiate the first dose of nPEP regimen

28-DAY REGIMEN — Recommended PEP Regimen:[b], Tenofovir 300 mg PO OD + Emtricitabine[d] 200mg PO ODplusRaltegravir 400 mg PO BD (*See Table4 for alternative regimens)*

↓

STEP 4: Baseline testing

BASELINE TESTING OF EXPOSED PERSON: • HIV test* • Pregnancy test for women • GC/CT NAAT (based on site of exposure) • RPR for syphilis • FBC/RP/LFT ** nPEP should not be continued in those who decline baseline HIV testing*	+	SOURCE TESTING, if source is available: • Obtain consent for HIV testing (if source patient's HIV status is unknown) • Obtain HIV test (preferably with turnaroundtime <1 hour) • If the test results are not immediately available, continue exposed person's nPEP while awaiting results • If the source person's HIV screening test Resultis negative but there may have been exposureto HIV in the previous 6 weeks, obtainplasmaHIV RNA assay • Continue exposed person's nPEP until results of the plasma HIV RNA assay are available

STEP 5: Provide risk reduction counselling

- Provide risk-reduction and primary prevention counselling
- Refer for mental health and/or substance use programs when indicated; consider need for intensive risk reduction counselling services and discuss future use of PrEP with persons with ongoing risk behaviour

[a]**Decisions to initiate nPEP beyond 72 hours post-exposure is not recommended**[13, 28], with the realization of diminishedefficacy when timing of initiation is prolonged; assess for hepatitis B and C; recommend serial HIV testing at 0, 4, and 12 weeks; provide risk-reduction counselling.

[b] If the source is known to be HIV-infected, information about his/her viral load, ART medication history, and history ofantiretroviral drug resistance should be obtained when possible to assist in selection of a PEP regimen. Initiation of the firstdose of PEP should not be delayed while awaiting this information and/or results of resistance testing. When thisinformation becomes available, the PEP regimen may be changed if needed in consultation with an experienced provider.

[d] Lamivudine 300 mg PO od may be substituted for emtricitabine. A fixed-dose combination is available when tenofovir isused with emtricitabine (Tenvir-EM).

Adapted fromBASHH UK guideline for the use of HIV post exposure prophylaxis following sexual exposure (PEPSE) 2015

Notes:

Needle stick injuries in non-healthcare settings (usually discarded needles)

- Potential risk evaluation should include prevalence of HIV in the community

PEP is generally not recommended in these settings as:

- Risk of HIV transmission through dried blood is extremely low.[17]

- The HIV status of the source is difficult to ascertain
- Do not test discarded needle for HIV, as yield is very low
- Consider vaccination for tetanus and Hepatitis B +/- HBV immunoglobulin

HIV exposure through bites

- Consider nPEP if biter or the bitten (or both) are exposed to the blood of the other

16.3 Baseline HIV testing for the exposed patient

- Test for HIV within 3 days of exposure – patients should be tested on the same day and before being given a course of nPEP
- Do not wait for results to give the initial dose of nPEP
- If this initial test is subsequently found to be positive, continue nPEP until a confirmatory test assay is viewed
- Decision to continue treatment will be based on current guidelines, and should be made in consultation with an ID Physician - it is likely now that we would just continue ART and not stop ART in these circumstances where the patient is found to be HIV positive

Testing for other STIs

- Ask for symptoms and test accordingly
- Consider screening with NAATs in asymptomatic patients for NG and CT (if available), based on site of exposure and serological screening for syphilis
- Don't forget to counsel patient about the risk of acquiring STIs

Pregnancy testing and emergency contraception

- All females should be tested for pregnancy
- Emergency contraception should be discussed and offered

Testing for Hepatitis B infection (HBV)

- ✓ Obtaining hepatitis B serology (HBsAg, hepatitis B surface antibody [anti-HBs], and hepatitis B core antibody [anti-HBc]) will identify nonimmune persons who should be provided hepatitis B vaccination.[13]
- ✓ In those who have not been vaccinated, give the first dose of HBV vaccination on the same day whilst waiting for results.

Testing for Hepatitis C infection

- Test for Hepatitis C antibody (Anti HCV)

16.4 Behavioural Intervention and Risk-Reduction Counselling

Recommendations:

- The clinician or a member of the HIV care team should provide risk-reduction counseling and primary prevention counseling whenever someone presents for nPEP.
- Clinicians should assess for emotional, psychological, and social factors that can contribute to risk behavior, such as depression, history of sexual abuse, and drug and alcohol use.

- Clinicians should refer patients to mental health and/or substance use programs when indicated and should consider the need for intensive risk-reduction counseling services.
- Patients who present with repeated high-risk behaviour should be considered for intensive risk reduction counseling and initiation of pre-exposure prophylaxis (PrEP).

16.5 Timing of nPEP

Ideally should be initiated as soon as possible after exposure, preferably within 24 hours, but can be considered up to 72 hours

16.5.1. Duration of nPEP: 28 days

NOTE

- If exposed person's baseline HIV rapid test is positive (and patient is already on nPEP), nPEP regimen should not be discontinued until the positive result is repeated with a 4th generation HIV test and pending review by ID Physician
- If the exposed person's week 4-6 post-exposure HIV test results are indeterminate or the exposed person has symptoms suggestive of acute HIV infection, clinicians should continue nPEP beyond 28 days until a definitive diagnosis is established
- When the source person is confirmed to be HIV-negative, clinicians should discontinue the nPEP regimen before completion
- High level of sustained adherence to nPEP is necessary to reduce the risk of transmitting HIV and decrease the risk of developing drug resistance

16.6 Recommended regimes

Recommended Regime for HIV PEP Following Non-Occupational Exposure

Tenofovir 300 mg PO daily + Emtricitabine 200 mg PO daily Plus Raltegravir 400 mg PO twice daily
Notes: <u>Rationale for recommended PEP regimen</u>: • Acts before viral integration with cellular DNA – this may pose a theoretical advantage but is not a reason why integrase inhibitors areused preferentially • Increased rates of adherence and completion[21, 22] • Favourable tolerability[23, 24] • Ease of administration • Favourable side effect profile, • Fewer potential drug-drug interactions, <u>When the source is known to be HIV-infected:</u> • Past and current ART experience, viral load data, and genotypic or phenotypic resistance data (if available) may indicate the use of analternative PEP regimen. • Consult with a clinician experienced in managing PEP.

Renal insufficiency:

• The dosing of tenofovir and emtricitabine/lamivudine should be adjusted in patients with baseline creatinine clearance<50 mL/min.

• Alternative regimen using combivir (zidovudine + lamivudine) may be used.

• Tenofovir should be used with caution in exposed persons with renal insufficiency or who are taking concomitant nephrotoxic medications

Adapted fromBASHH UK guideline for the use of HIV post exposure prophylaxis following sexual exposure (PEPSE) 2015

Alternative regimes

NRTI backbone (2 drugs)	**Third agent**
Combivir 1 tablet BD (Zidovudine 300mg + Lamivudine 150mg)	Kaletra 2 tablets BD (Lopinavir 200mg + Ritonavir 50 mg) **OR** Atazanavir/Ritonavir (300mg/100mg) once daily OR Dolutegravir 50 mg daily

Notes:

• Three-drug regimen preferred:

- ✓ Consistent with ARV treatment practices
- ✓ 3 drug ARV regimens are associated with better virological suppression than 2 drug regimens in studies of ARVs in treatment of established HIV infection
- ✓ Provides greater protection against resistant virus than 2 drug regimens
- ✓ Provides consistency across PEP guidelines

• The use of a two-drug regimen would be preferred to discontinuing the regimen completely if tolerability is a concern.

16.5.3. nPEP in pregnancy

- Based on increasing clinical experience with ART, nPEP is indicated at any time during pregnancy when a significant exposure has occurred, despite possible risk to the woman and the fetus.
- Expert consultation should be sought.
- Recommended PEP regimen is the same for pregnant women as for non-pregnant adults
- Clinician should discuss the potential benefits and risks to her and to the fetus.
- Pregnant women presenting for nPEP as a result of risky behavior should be the focus of Intensified education and prevention interventions.
- After completion of the 28-day nPEP regimen, initiation of pre-exposure prophylaxis (PrEP) should be considered.

Table 16.2 Anti retroviral drugs to avoid as nPEP

Drugs to avoid	**Rational**
Efavirenz	●CNS side effects which may impact on adherence and ability to work ●concerns around EFV resistance in community HIV isolates
Nevirapine	●Contraindicated for use in PEP due to potential for severe hepatotoxicityand risk of severe rash
Abacavir	●Potential for hypersensitivity reactions
Stavudine, didanosine	●possibility of toxicities

Table 16.2 Follow-up and monitoring

Test	Source	Exposed persons			
	Baseline	Baseline	4–6 weeks after exposure	3 months after exposure	6 months after exposure
		For all persons considered for or prescribed nPEP for any exposure			
HIV Ag/Ab testing a (or antibody testing if Ag/Ab test unavailable)	√	√	√	√	√[b]
Hepatitis B serology, including: hepatitis B surface antigen hepatitis B surface antibody hepatitis B core antibody	√	√	-	-	√[c]
Hepatitis C antibody test	√	√	-	-	√[d]
	For all persons considered for or prescribed nPEP for sexual exposure				
Syphilis serology[e]	√	√	√	-	√
Gonorrhea[f]	√	√	√[g]	-	-
Chlamydia[f]	√	√	√[g]	-	-
Pregnancy[h]		√	√	-	-

Abbreviations: Ag/Ab, antigen/antibody combination test; HIV, human immunodeficiency virus; nPEP,nonoccupational postexposure prophylaxis; tenofovir DF, tenofovir disoproxil fumarate.

a Any positive or indeterminate HIV antibody test should undergo confirmatory testing of HIV infection status.

b Only if hepatitis C infection was acquired during the original exposure; delayed HIV seroconversion has been seen in persons who simultaneously acquire HIV and hepatitis C infection.

c If exposed person susceptible to hepatitis B at baseline.

d If exposed person susceptible to hepatitis C at baseline.

e If determined to be infected with syphilis and treated, should undergo serologic syphilis testing 6 months after treatment

f Testing for chlamydia and gonorrhea should be performed using nucleic acid amplification tests. For patients
diagnosed with a chlamydia or gonorrhea infection, retesting 3 months after treatment is recommended.

- For men reporting insertive vaginal, anal, or oral sex, a urine specimen should be tested for chlamydia and gonorrhea.
- For women reporting receptive vaginal sex, a vaginal (preferred) or endocervical swab or urine specimen should be tested for Chlamydia and gonorrhea.
- For men and women reporting receptive anal sex, a rectal swab specimen should be tested for Chlamydia and gonorrhea.
- For men and women reporting receptive oral sex, an oropharyngeal swab should be tested for gonorrhea. (http://www.cdc.gov/std/tg2015/tg-2015-print.pdf)

g If not provided presumptive treatment at baseline, or if symptomatic at follow-up visit.

h If woman of reproductive age, not using effective contraception, and with vaginal exposure to semen.

i eCrCl = estimated creatinine clearance calculated by the Cockcroft-Gault formula; eCrClCG = [(140 − age) x ideal body weight] ÷ (serum creatinine x 72) (x 0.85 for females).

Adapted from Updated Guidelines for Antiretroviral Postexposure Prophylaxis After Sexual, Injection Drug Use, or Other Nonoccupational Exposure to HIV— United States, 2016 from the Centers for Disease Control and Prevention, U.S. Department of Health and Human Services

Notes:

- HIV, STI, HBV and HCV screening recommended even if nPEP is declined
- Repeat HIV testing at 4-6 weeks and 3 months after exposure should be performed with laboratory-based test (4th generation HIV test) rather than POC test
- HIV testing at 4- 6 weeks and 3 months is recommended after significant exposures, regardless of whether the individual accepts or declines PEP treatment
- Consider re-evaluation within 3 days of the exposure to further clarify the nature of the exposure, review available source person data, evaluate adherence, and monitor toxicities associated with the PEP regimen

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Chapter 17: PRE EXPOSURE PROPHYLAXIS (PrEP)

17.1 Introduction

Pre-Exposure Prophylaxis (PrEP) is when an HIV-negative person at substantial risk of HIV infection takes TDF and (FTC or 3TC) to prevent him/herself from contracting the virus. It is a temporary method for reducing the chances of contracting HIV during phases of high-risk behaviour. Efficacy of PrEP ranges from 44% to 86% and is highly dependent on adherence.[1-4]

The decision to start PrEP should be made after a detailed assessment to ensure that patient is not infected with HIV (i.e. paying attention to symptoms of acute infection and awareness of the window period of the HIV test) and after the patient, fully understands the limitations of PrEP and the required adherence. More than one review may be required prior to starting PrEP and PrEP should always be used as part of a package of HIV prevention services which includes provision of condoms and lubricants as contraception, regular HIV testing, STI management and risk reduction counselling

17.2 Eligibility for PrEP

17.2.1 Who would you recommend PrEP?

Table 17.0 Eligibility criteria for PrEP[5&6]

- HIV seronegative, and no suspicion of acute HIV infection (that is, RNA or antigen present before seroconversion)
- Substantial risk for HIV infection (by history in the last 6 months)
    - Sexual partner with HIV who has not been on effective therapy for entire 6 months, OR Sexually active in a high HIV prevalence population (define high prevalence population) AND any of the following:
        - Vaginal or anal intercourse without condoms with more than one partner, OR
        - A sex partner with one or more HIV risk factors, OR
        - A history of an STI by lab testing or self-report or syndromic STI treatment, OR
        - Use of stimulant drugs
        - Commercial sex work
        - Any sharing of injection materials with other people, OR
        - Any use of non-occupational post-exposure prophylaxis (nPEP).
- No contraindications to Tenofovir or Emtricitabine
- Willingness to use PrEP as prescribed

17.3 The sexual partner of someone who is not on suppressive ART.

ART that suppresses the viral load in the infected partner is highly effective in preventing transmissions to others. However, PrEP can provide additional protection in certain situations:

1. As a bridge when the HIV infected partner has been taking ART for less than 6 months (ART can take 3-6 months to suppress viral load)
2. The uninfected partner is unsure about the HIV status of their partner or whether their viral load is suppressed.

17.4 Prescribing PrEP

17.4.1 What should you prescribe for PrEP? [5]

TDF 300mg + (FTC 200mg or 3TC 300mg) PO per day

- This could be a single combination tablet Tenvir-EM (200mg/300mg) once a day.
- We do not recommend giving a prescription longer than 3 months.

17.4.2 Contraindications for the use as PrEP

- CrCl of <50ml/min
- HIV + or evidence of possible acute HIV infection
- Known allergies to any of the PrEP components
- Unable or unwilling to return for 3 monthly HIV testing, counselling and safety monitoring visits

17.4.3 Key efficacy messages

- Highly effective for preventing HIV infection when adherent
- At least 7 days of PrEP are needed before achieving full protection
- At least 5 to 7 days of PrEP are needed before achieving full protection for anal intercourse and nearly 20 days of PrEP are needed before achieving full protection for vaginal intercourse (based on preliminary pharmacological study) [7]
- It doesn't prevent other STIs (GC/CT/syphilis/genital warts/HCV)
- The iPERGAY study showed that on-demand PrEP can also be effective. However, this needs to be interpreted carefully because the study was limited to men who have sex with men and requires taking PrEP 24 to 2 hours before having intercourse then 24 and 48 hours after. [3]

17.4.4 Adverse effects[8]

- 4-10 % may have GI side-effects (usually resolves over the first month) [5]
- 0.7 %may develop AKI[8]
  - 1 % whose serum creatinine increased > 120 micromol/L,[9] after discontinuation renal function usually recovers [10]
  - Fanconi syndrome <0.1%more likely to be reversible if picked up early [11]
- 0.5 – 1.5% loss of bone mineral density occurs within the first 6 months (recovers after stopping PrEP)[12&13]

17.5 Pre-PrEP counselling& assessment[5&6]

17.5.1 Education

1. Patient must be made aware of the limitations of PrEP
   - The importance of adherence
   - Lack of protectiveness against STI and pregnancy
   - Doesn't offer 100% protection against HIV
   - It is possible to cycle off oral PrEP when moving out of "seasons of risk"–it is not meant to be lifelong therapy
2. Discussion about start-up syndrome.
   - Such as nausea, abdominal cramping or headache, that are typically mild and self-limited and do not require discontinuing PrEP
   - These symptoms usually resolves after a few weeks of starting
   - A discussion at the beginning may help adherence
3. Discuss adverse effects including long-term safety
   - Include potential but undemonstrated risk of birth defects if taken by a women
4. Confirm schedule for follow-up, with a HIV test at least every 3 months
5. Educate on symptoms of HIV sero-conversion
6. Stress the importance of adherence and adherence support

17.5.2 Assessment

1. Screen for symptoms of acute HIV infection within the past 6 weeks
2. Review patient's current medication list for interactions.
3. Evaluate willingness to take PrEP daily.
4. Is the patient involved with HIV-seropositive sexual partners?
   - Are any HIV-seropositive sexual partners taking ART?
   - Are resistance data available?
5. Does the patient have the means to pay for PrEP?
6. Evaluate fertility goals and contraception use in women who are PrEP candidates.

17.6 Laboratory evaluation

17.6.1 Initial laboratory testing

1. Baseline HIV testing - stress the importance of ruling out pre-existing HIV infection
   - Third or fourth-generation HIV test (preferable to use 4th generation lab test)
   - NAAT (e.g. viral load) for HIV in:
     a. Patients with symptoms of acute infection (influenza or cold-like symptoms)
     b. Patients whose HIV antibody test results are negative but who have reported engaging in unprotected sex with an HIV-infected partner or partner of unknown HIV status within the past month

Note: Drug-resistant HIV is more likely to occur in patients who initiate PrEP with undiagnosed acute HIV infection. There is also an ongoing potential for drug resistance to develop in those taking suboptimal PrEP who become infected whilst on PrEP.

- Basic metabolic panel – renal function test and liver function test
- PrEP should not be initiated for patients with a creatinine clearance <50 mL/min

2. Urinalysis
    - Proteinuria can be an early warning sign of tenofovir toxicity
    - Baseline urinalysis should be used to identify any pre-existing proteinuria
3. Serology for Hepatitis A, B and C viruses (Hep A IgG, Hep B sAg , Hep B sAb and Hep B core Ab, Hep C Ab)
    - Hepatitis B vaccination should be provided to susceptible patients who are Hep B sAg and sAb neg

Note: Be aware that Hepatitis B is treated by the components of PrEP and can flare when PrEP is stopped, patients with detectable HBsAg and ALT elevated more than twice the upper limit of normal or clinical signs of cirrhosis could benefit from long-term therapy for hepatitis B infection.

4. STI screen
    - Ask about symptoms of STIs (e.g. sore throat, dysuria, vaginal or penile or rectal discharge, genital ulcers)
    - NAAT for gonococcal (GC) and chlamydial(CT) infections3-site screening based on exposure (genital, rectal, pharyngeal); or standard tests (GC - culture/CT – EIA/DFA) based on local practice if NAAT unavailable
    - Rapid plasma reagin test for syphilis
5. Pregnancy testing
    - If a woman is pregnant while taking PrEP, known risks and benefits should be discussed.

17.7. Post-PrEP Follow-Up[5&6]

1. We suggest that patient be reviewed 4 weeks after initiation of PrEP to assess tolerability and side effects and laboratory screening for renal impairment or Fanconi's syndrome (renal profile and urinalysis).
2. Subsequently follow-up should be at least every 3 months.
    - At the 3 monthly follow-up
        - Assess the indication for PrEP and adherence
            - It is possible to cycle off oral PrEP when moving out of "seasons of risk"–it is not meant to be lifelong therapy
        - Laboratory testing for
            - Serum creatinine and creatinine clearance (this can actually be done at the 3 month follow up and thereafter every 6 months –WHO recommendations, more frequently in those with other risk factors for kidney disease)
            - HIV testing with either a third or fourth generation HIV test (4th generation lab test preferable)
3. Every 6 months you should also consider screening the patient for STIs.
4. In patients wishing to stop PrEP, as with PEP; PrEP can be discontinued 28 days after the last exposure to infected fluid.
5. Consider every visit as an opportunity to provide Risk Reduction Counselling

17.8 Management of special situations

1. Creatinine elevation: consider discontinuing PrEP if creatinine elevation is persistent on a second sample and creatinine clearance < 50 ml/min. Recheck creatinine in another 1 to 3 months and PrEP can be restarted if renal function, as measured by CrCl, has returned to >50 ml/min
2. Seroconversion while receiving PrEP: offer ART as soon as possible without a gap after discontinuation on PrEP even while confirmatory test is underway. A referral to a tertiary center can be done for PrEP providers who are not comfortable starting ART.
3. There are no known interactions between PrEP and hormonal contraceptives.
4. In patients with recurrent HIV exposure requiring nPEP, consider transitioning to PrEP after 28 days of PEP.
5. The use of PrEP in pregnancy and breastfeeding needs to be weighed against the risk of transmitting HIV to the child if the mother becomes infected while pregnant or breastfeeding.

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Annex 1. WHO Clinical Staging of HIV/AIDS for 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 109 /l) and/or chronic thrombocytopenia (below 50 x 109 /l)
CLINICAL STAGE 4* HIV wasting syndrome Pneumocystis jeroversii 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

*Some additional specific conditions can be included in regional classifications, such as penicilliosis in Asia, HIV-associated rectovaginal fistula in southern Africa and reactivation of trypanosomiasis in Latin America.

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 These ARV combinations will increase K65R TDF + 3TC + ddI	These ARV combinations will increase K65R TDF + 3TC + ddI 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

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 (Abacavir: Child-Pugh Score: 5–6 = 200mg BID (use oral solution); > 6 = contraindicated)
Zidovudine (AZT)	250 mg or 300 mg twice daily1 Take without regard to meals
Emtricitabine (FTC)	200 mg once daily Take without regard to meals
Lamivudine (3TC)	150 mg twice daily or 300 mg once daily Take without regard to meals
Tenafor (TDF)	300 mg daily Take without regard to meals
NonNucleoside RTIs (NNRTIs)	
Efavirenz (EFV)	600 mg once daily Take on an empty stomach to reduce side effects
Etravirine (ETV)	200 mg twice daily
Nevirapine (NVP)	200 mg once daily for 14 days, followed by 200 mg twice daily Take without regard to meals
Rilpivirin	25 mg (one 25 mg tablet) taken once daily with a meal

Protease Inhibitors (PIs)	
Atazanavir/ ritonavir (ATV/r)	300 mg/100 mg once daily2 ritonavir (ATV/r) Take with food Dosage adjustment in hepatic insufficiency (Atazanavir: Child-Pugh Score: 7–9 = 300mg once daily; >9 = not recommended)
Darunavir + ritonavir (DRV/r)	600/100 mg twice daily Take with food
Lopinavir/ritonavir (LPV/r)	400 mg/100 mg twice daily **Considerations for individuals receiving TB therapy** In the presence of rifabutin, no dose adjustment required. In the presence of rifampicin, adjusted dose of LPV/r: (LPV 800 mg + RTV 200 mg twice daily or LPV 400 mg + RTV 400 mg twice daily).or, SQV/r (SQV 400 mg + RTV 400 mg twice daily), with close monitoring.
Integrase strand transfer inhibitors (INSTIs)	
Dolutegravir (DTG)	50 mg once daily
Raltegravir	400 mg twice daily

Annex 4 • Dosage Adjustment for ARTS in Renal Impairment

Drug adjustments are based on patient's estimated creatinine clearance

ART	**Adjustment for Renal Failure (Crcl) Ml/MIN**			**Hemodialysis, CAPD**	**Comments & Dosage for CRRT**
	>50 – 90	10 – 50	<10	HEMO: Dose AD; CAPD: No Data; CRRT: 100mg 1ST day, THEN 50mg/day	
LAMIVUDINE	300mg q24h	50- 150mg q24h	25-50 q24h		
MARAVIROC	300mg bid	No data	No data	Increased risk of side effects if maraviroc+CYP3A inhibitor and CrCl<50	
TENOFOVIR	300mg q24h	300mg q48h	Not recommended	Not recommended	
Zidovudine	300mg bd	300mg bd	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	Atazanavir
Abacavir	Lopinavir
Efavirenz	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 minima 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	8 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
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
Lactate	<2.0 ULN Increased without acidosis	>2.0 ULN Increased without acidosis	Increased lactate with pH with pH <7.3 without life-threatening consequences	Increased lactate pH <7.3 without life-threatening consequences consequences
Creatinine	>1.0 – 1.5 x ULN	>1.5 – 3.0 x ULN	>3.0 – 6.0 x ULN	>6.0 x ULN