Malaysian Consensus Guidelines on Antiretroviral Therapy 2022

MALAYSIAN SOCIETY FOR HIV MEDICINE

MINISTRY OF HEALTH MALAYSIA

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Abbreviations

1HP	daily isoniazid and rifapentine for one month
3HP	weekly isoniazid and rifapentine for three months
3HR	daily isoniazid and rifampicin for 3 months
3TC	lamivudine
4R	daily rifampicin for 4 months
6H	daily isoniazid for 6 months
9H	daily isoniazid for nine months
ABC	abacavir
AFP	alpha-fetoprotein
APRI	aspartate aminotransferase to platelet ratio index
ART	antiretroviral therapy
ARV	antiretroviral (drug)
ATV	atazanavir
AZT	zidovudine
BMI	body mass index
cART	combination antiretroviral therapy
CSF	cerebrospinal fluid
CNS	central nervous system
d4T	stavudine
DAA	direct-acting antiviral (drug)
DCV	daclastavir
DDI	drug-drug interactions
DM	diabetes mellitus
DRV	darunavir
DTG	dolutegravir
EFV	efavirenz
ELISA	enzyme-linked immunosorbent assay
ETV	etravirine
FIB-4	fibrosis 4 score
FPV	fosamprenavir
FTC	emtricitabine
HBV	hepatitis B virus
HCC	hepatocellular cancer
HCV	hepatitis C virus
HPT	hypertension
HPV	human papillomavirus
HSV	herpes simplex virus
IDV	indinavir
IFN	interferon
INSTI	integrase strand transfer inhibitor (also known as integrase inhibitor)
IPT	isoniazid preventive therapy
IRIS	immune reconstitution inflammatory syndrome
LPV	lopinavir
LPV/r	lopinavir/ritonavir
NAT	nucleic acid amplification testing
NFV	nelfinavir
NNRTI	non-nucleoside reverse-transcriptase inhibitor
NPEP	non-occupational post exposure prophylaxis
NPRA	national pharmaceutical regulatory agency
NRTI	nucleoside reverse-transcriptase inhibitor
NVP	nevirapine
PCR	polymerase chain reaction
PEP	post-exposure prophylaxis
PI	protease inhibitor
PJP	pneumocystis jirovecii pneumonia
PLWH	person living with HIV
PrEP	pre-exposure prophylaxis
RAL	raltegravir
RVD	ravidasvir
RT	reverse transcriptase
RTV	ritonavir
/r	low dose ritonavir
RPV	rilpivirine
SOF	sofosbuvir
SVR	sustained virological response
TAF	tenofovir alafenamide
TB	tuberculosis
TDF	tenofovir disoproxil fumarate
ULN	upper limit of normal
USS	ultrasonogram
VL	viral load

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This document is available for download at **https://www.mashm.net**

CHAPTER 1

INTRODUCTION

Since 1996, the management of Human Immune Deficiency Virus (HIV) infection has been revolutionized with antiretroviral therapy (ART), usually consisting of three or more antiretroviral (ARV) drugs that act on different targets in the virus.[1] ART is synonymous with combination antiretroviral therapy (cART). ART has dramatically reduced opportunistic infection-related mortality among HIV infected persons, improved quality of life and survival. With ART, HIV has become a chronic manageable disease. The primary goal of this guideline is to provide HIV care practitioners with recommendations based on current knowledge of ARV used for the treatment of HIV-infected adults in Malaysia. Clinical decisions regarding starting ART in HIV affected individuals should be tailored according to patient's circumstances.

1.0 What is New in this Guideline Compared to the 2017 Guideline?

Relevant chapters have been reviewed and updated based on the most current information and evidence.

1.1 Factors to Consider Before 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 inflammatory syndrome (IRIS)
3. The ART options that are available locally
4. Underlying medical diseases such as cardiovascular disease, diabetes mellitus, dyslipidaemia, and depression
5. Possible drug-drug interactions, dosing frequency and pill burden
6. Risk of primary resistance, i.e. the acquisition of HIV infection from a partner who is already on ART
7. Individual factors that may hinder adherence such as irregular working hours and social support.

1.2 Goals and Benefits of ART

ARVs cannot eradicate HIV from the human body nor cure HIV infection. The goals and benefits of ART include:

1. Reduce HIV related morbidity and mortality
2. Improve quality of life
3. Increase lifespan[2,3]
4. Restore and preserve immunologic function
5. Maximally and durably suppress viral load (VL)
6. Prevent HIV transmission to uninfected sexual partner and the unborn child
7. Prevent emergence of HIV drug resistance

1.3 Treatment Outcomes may be measured from three Aspects:

1. Clinically by the reduction in the number and frequency of opportunistic infections (OIs) and improvement of general wellbeing
2. Immunologically by gradual and steady rise in CD4 T-cell counts
3. Virologically by a decrease in VL, ideally by achieving virological suppression at six months after initiation of treatment.

1.4 ARV Drugs Available in Malaysia

ART options have expanded greatly since the first drug zidovudine was approved in the US in 1987. Currently, there are four classes of ARV drugs which target different phases in the HIV life cycle (see Table 1.0).

Table 1.0 • Antiretroviral drugs currently available in Malaysia

Class	Abbreviation
Nucleoside or nucleotide reverse transcriptase inhibitors (NRTI)	
Abacavir	ABC
Emtricitabine	FTC
Lamivudine	3TC
Stavudine	d4T
Tenofovir disoproxil fumarate	TDF
Zidovudine	AZT or ZDV
Non-nucleoside reverse transcriptase inhibitors (NNRTI)	
Efavirenz	EFV
Etravirine	ETV
Nevirapine	NVP
Rilpivirine	RPV
Protease Inhibitors (PI)	
Atazanavir	ATV
Darunavir	DRV
Lopinavir / ritonavir	LPV/r
Ritonavir	RTV
Integrase Inhibitors	
Raltegravir	RAL
Dolutegravir	DTG

*Stavudine has been recommended to be phased out by WHO due to side effects since 2010

1.5 Fixed Dose Combinations

Fixed dose combinations (FDC) are multiple ARVs combined into a single tablet (see Table 1.2). FDC reduces pill burden and cost. Dosing simplification improves adherence and will lead to durable virological suppression.[3,4]

Table 1.1 • Fixed Dose Combinations Registered in Malaysia

Fixed Dose Combinations
Abacavir/Lamivudine (ABC/3TC)
Abacavir/Lamivudine/Zidovudine (ABC/3TC/AZT)
Lopinavir/Ritonavir (LPV/r)
Tenofovir disoproxil fumarate/emtricitabine (TDF/FTC)
Zidovudine/Lamivudine (AZT/3TC)

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CHAPTER 2

ASSESSMENT OF ADULTS LIVING WITH HIV

All adults with HIV infection entering into care should have a complete medical history, physical examination, baseline laboratory evaluation and counselling about the HIV infection. [1] The goals of the initial evaluation are: -

1. To confirm the diagnosis of HIV infection
2. To identify risk factors related to HIV acquisition
3. To obtain appropriate baseline historical data and a comprehensive medical review of symptoms
4. To perform a thorough physical examination looking for clinical manifestations of HIV infection and evaluation of other co-infections
5. To ensure patient's understanding of HIV infection and its mode of transmission
6. To assess social support and coping strategies
7. To initiate medical care

For treatment-experienced patients who present to a new health care provider, obtain a complete antiretroviral (ARV) history and review of past medical records. [2]

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

Table 2.0 • History Taking for HIV Positive Patient[2]

	Symptoms / Components	Significance
History of Presenting Complaint	– Constitutional symptoms: fever, loss of weight and loss of appetite – CNS: headache, dizziness and headache – GIT: oral thrush, odynophagia, diarrhoea and rectal bleeding – Respiratory: chronic cough and shortness of breath especially on exertion. – Skin lesions: may suggest bacterial/ fungal/ Mycobacterium/ scabies, viral, malignancy and mites. – Soft tissue swellings: may suggest lymphadenopathy, tumour or abscess. – Genitourinary: urethral discharge or genital ulcers suggestive of STIs. – Eye symptoms: blurring of visions, diplopia, floaters (CMV, Toxoplasmosis)	Diagnosis of opportunistic infection or co-infection

	Symptoms / Components	Significance
Drug History	Current medications & dosages Alternative medications/supplements Smoking & Alcohol Recreational drugs use Drug addiction Use of Pre or post exposure prophylaxis	Allergy Potential drug-drug interaction
Past & Current Medical Surgical, Obstetrics & Gynaecology History	TB, hepatitis, herpes, varicella, (Syphilis, gonorrhoea, Chlamydia) DM, IHD, HPT, Renal disorder, Dyslipidaemia. Treatment received or completed for the above. Vaccination history Last negative HIV test. Blood donation within a year of diagnosis	Risk of worsening condition due to ARVs, concomitant drug-drug interaction and co-infection Alert the local blood bank
Psychosocial History	Circle of confidentiality Partner & children Support network Occupation, housing, mental health issues	
Sexual & Reproductive History	Sexual history & practices Safer sex & risk reduction Partner status & disclosure issue Participation in chemsex	Transmission prevention measures e.g PMTCT treatment, PrEP or NPEP
Family History	History of DM/HPT/Cardiovascular diseases	Requires counselling Increases risk in patient

Table 2.1 • Important Laboratory Investigations[2]

Evaluation	Investigations	Specific Tests	Entry to Care	At Follow-up on ART	Comments
HIV Disease	All referred cases of HIV infection need a confirmatory test				
	Plasma HIV RNA	HIV viral load	√	Every 4 to 6 months after initiation of ART. Annually if stable	
	CD4		√	Refer section 2.1	If CD4 count is • <200, test 3 to 6 monthly • 200 – 350, test annually • >350 on 2 occasions 1 year apart, no further CD4 count required
Co-infections	Syphilis serology	VDRL/RPR/ TPHA	√	Annual screening if at risk	
	Hep A Serology for "at risk group" if test is available in the facility	Hep A IgG	AT RISK GROUP		risk group: MSM vaccination if non immune
	Hep B Serology	Hepatitis B surface antigen (HbsAg) Hepatitis B surface antibody (HbsAb)* (if test is available in the facility)	√	Annual screening if at risk	Vaccinate if non -immune.
	Hep C Serology	HCV Antibody	√	Annual screening if at risk	
CXR			√	When clinically indicated	To look for active TB (initiate IPT if no active tuberculosis)
Hematology	FBC		√	Every 4 to 6 months	If initiated on AZT, FBC should be repeated at 4,8 and 12 weeks of initiation or if symptomatic of anemia
CVS	ECG		√ *	When clinically indicated	*If patient has other risk factors for IHD
Metabolic	Fasting Lipid Profile		√	Every 6 to 12 months	EFV, NRTIs, PIs (with the exception of unboosted atazanavir), can cause insulin resistance and dyslipidaemia
	Fasting Blood Sugar		√	Every 6 to 12 months	

Evaluation	Investigations	Specific Tests	Entry to Care	At Follow-up on ART	Comments
Liver	ALP, AST, ALT, Bilirubin, Albumin		√	Every 4 to 6 months	NRTI and NNRTI can cause hepatotoxicity. If on NVP, ALT need to be monitored more frequently at baseline, 2, 4, 12 weeks and then every 3 to 6 months. Obtain ALT in patients with new onset rash
Renal	Renal function / eGFR		√	At week 4, 8, and 12 upon initiation of Tenofovir (TDF), 4 to 6 months if stable	TDF may cause renal tubular dysfunction. Routine monitoring of calculated creatinine clearance should be performed for all patients on TDF during follow up
	Urine for dipstick		√		
Others	HLA-B*5701		X	Selected cases initiated on abacavir	Discuss with ID physician
	Cervical/PAP Smear for women	Pap smear	√	Annually if the results of the 3 consecutive pap smear 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 counts that averages 50 –150 cells/mm per year until a threshold is reached. However, some patients may experience a slower increase CD4 cell counts particularly when ART was 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 still less than 200 cells/mm^3, test the CD4 every 3 to 6 monthly. When the CD4 reaches 200 to 350 cells/mm^3, test the CD4 annually. Once the CD4 is more than 350 on 2 occasions 1 year apart, no further CD4 count is required unless treatment failure is suspected.

HIV Viral Load

HIV viral load is more accurate and reliable than CD4 cell counts to monitor treatment response and for early detection of treatment failure.

HIV Viral Load should be performed:

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

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 200 copies/mL by 6 months . A 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.

Monitoring Other Parameters (Refer Table 2.1)
The frequency of monitoring depends on the response to ART and the choice of drugs. At the minimum monitoring should take place at 2- 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 needs to be complemented by assessment of treatment side effects and adherence.

2.2 Co-Trimoxazole Prophylaxis (Refer Table 2.2)

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

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%	T. Bactrim one double -strength (DS) tablet or two single-strength (SS) tablets once daily Total daily dose is 960 mg (800 mg sulfamethoxazole plus 160 mg trimethoprim)	When CD4 >200 for two consecutive readings Or When CD4 100-200 AND HIV-VL is undetectable more than once
2. Oropharyngeal candidiasis		
3. Opportunistic infections /AIDS defining illness		PLHIVs initiated on ART after anti TB and have achieved viral load suppression and CD4 more than 200 cells/ uL, co-trimoxazole prophylaxis may be terminated. For those initiated on antiTB while already on ART with suppressed viral load and CD4 more than 200 cells/uL, co-trimoxazole prophylaxis may not be necessary.
4. Patient who has completed successful treatment for PJP		

Co-Trimoxazole in Pregnant / Lactating Women

Women who fulfil the criteria for co-trimoxazole prophylaxis should be continued throughout their pregnancy. If co-trimoxazole prophylaxis is required during pregnancy, it should be started regardless of the stage of pregnancy.

Contraidications to Co-Trimoxazole Preventive Therapy

Co-Trimoxazole is absolutely contraindicated in severe allergy to sulfa-containing drugs and relatively contraindicated in severe liver disease, severe anaemia or severe pancytopenia. As an alternative, dapsone at a dose of 100 mg daily may be used (G6PD test must be normal prior to initiation).

Co-Trimoxazole Desensitization (refer table 2.3)

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

Step	Dose
Day 1	80 mg SMX + 16 mgTMP (2 ml oral suspension)
Day 2	160 mg SMX + 32 mgTMP (4 ml oral suspension)
Day 3	240 mg SMX + 48 mgTMP (6 ml oral suspension)
Day 4	320 mg SMX + 64 mgTMP (8 ml 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
(Adopted from Consensus Guidelines on antiretroviral therapy 2014)

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CHAPTER 3

OPTIMIZING CARE AND MAXIMIZING BENEFITS OF ART

First line ART offers the best opportunity for effective viral suppression and immune recovery. It also improves mortality as it reduces AIDS related and non-AIDS related serious illnesses. In recent years, evidence has surfaced to prove the concept of HIV 'Undetectable = untransmittable' (U=U). Undetectable HIV viral load level will reduce HIV transmission risk to negligible or non-existent. Therefore U=U is not only a treatment aim but also an effective HIV prevention method.

3.1 Pre ART-Counselling

PLWH should be given opportunity in making decisions about their treatment. Studies have shown that good quality relationship and communication skills between clinician and PLWH are associated with better treatment outcome.

Before prescribing ART, clinician should assess PLWH individually on these matters:

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

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

3.2 ART Counseling

Currently, first line ART offers the best opportunity for effective viral suppression and immune recovery. ART also reduces the morbidity and mortality, improve quality of life and increase the life expectancy of patients on effective therapy.

- To educate patient on 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 (linked 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 ART

3.3 Rapid ART Initiation

Previous practise of ART initiation includes extensive patient preparation prior to starting ART. However, evidence from clinical trials have shown significant benefits of rapid ART initiation (within 7 days of diagnosis). Clinical trials on same-day ART initiation have shown superior results in improved clinical outcomes in viral load suppression, retention in care and survival. The concept of "to treat all people living with HIV regardless of CD4 cell counts" supports the rapid initiation of ART and this includes the offer of same-day initiation unless there is presence of clinical contraindications.

Individuals most likely to benefit from this approach include those with advanced HIV disease (to reduce the high risk of mortality in this group), pregnant women, and those with acute HIV infection (to decrease viral load and reduce the risk of virus transmission). However possible harms identified include potential of missing clinical conditions that require management before ART, risk of IRIS among severely immunosuppressed people and potential of people to feel coerced into starting ART when they are not ready psychologically.

When to Consider Rapid Initiation of ART

1. Willing and ready to start ART
2. No clinical signs and symptoms of active TB or other opportunistic infections
3. Advanced HIV disease
4. Pregnant women
5. Acute HIV infection

3.4 Adherence to ART

ART adherence is the key to successful treatment. An adherence to ART of 95% or more is believed to be the requirement to achieve optimal viral suppression. However meta-analysis show that adherence rates slightly below the threshold of 95% should not deter initiation of ART. Interventions to improve adherence are most likely to be successful when they are comprehensive and tailored to individual's socio-demographic background and behavioural characteristic.

Specific groups at risk of poor adherence includes:

- those with poor family support
- intravenous drug users
- adolescents
- pregnant mothers
- underlying psychiatric illness

Method of counselling on improvement of adherence must always be individualized.

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 patients' readiness to start ART	• Assess patient's attitude and belief regarding ART and adherence • Practice adherence to planned ART regime using 'vitamin training' may be considered • 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 • Scepticism about the effectiveness of 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 • Ask the patient open-ended questions *(e.g., In the last 3 days, please tell me how you took your medicines)* • Tracking pharmacy dispensing records to ensure uninterrupted supply of ART to patients
Identify the type of non-adherence	• Failure to fill the prescription(s) • Failure to take the right dose(s) at the right time(s)

Strategies	Examples
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

3.5 Increasing 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 health 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 preventing 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 another supplementary test i.e., different rapid HIV Ab/Ag test ± HIV PCR especially in asymptomatic patient and those who deny high risk behavior or exposure.

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 to 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.

Step 3 • Identify Clinics or Hospitals Nearest to Patient with HIV Service

Put in place convenient appointment arrangements with referral clinicians / counselor nurses 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. Treatment centers may also consider setting up virtual clinics for stable patients.

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.

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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STARTING ART

4.1 Initiating Antiretroviral Therapy (ARV)

Rapid ARV initiation (within 7 days of HIV diagnosis) or same day ARV initiation should be offered to all people living with HIV following a confirmed HIV diagnosis and clinical assessment. Rapid ARV initiation is especially important for people with very low CD4 cell count, for whom the risk of death is high. ARV initiation should be offered on the first visit to people who are ready to start treatment.

4.2 Timing of ARV in Opportunistic Infections (OIs)

Starting ART in the event of acute OIs remains a great challenge. The occurrence of drug–drug interactions, overlapping adverse effects, high pill burden, patient's adherence and paradoxical reactions may also pose problems. However delaying ARV till completion of therapy will increase the risk of progression to AIDS and death.

This guideline generally recommends clinical assessment at the end of 2 weeks of OI therapy. If patient is stable and has improved with OI treatment, initiation of ARV should not be delayed.

Table 4.1 • Examples of OIs that suitable for early ARV initiation[1-7]

Opportunistic Infection	Cd4 count	Initiation of ARV	Comments
General recommendation	Any	As soon as possible or within 2 weeks after starting treatment for OI	
Tuberculosis	<50 >50	within 2 weeks of starting TB treatment Treatment can be delayed up to 8 to 12 weeks of starting TB treatment	In patients with TB meningitis and low CD4 cell counts, early ART may pose a risk of life-threatening IRIS, careful monitoring and consultation with experts is strongly recommended. Please refer to the TB / HIV coinfection guidelines for detailed explanation
***Pneumocystis jirovecii* pneumonia (PJP)**	Any	ART should be initiated within 2 weeks	
CMV	Any	Treatment should be strongly considered to be started **at the second week** of CMV treatment	
Talaromycosis (Penicilliosis)	Any	ART should be initiated within 2 weeks	
Cryptococcal meningitis	Any	Delay initiation of ART at least until after completion of the induction/ consolidation phase (4-6 weeks).	Delay in ART may be particularly important in those with evidence of increased intracranial pressure / Low CSF WCC. If effective ART is to begin prior to 4-6 weeks, the treating physicians should be prepared to aggressively address complications caused by Immune Restoration Syndrome (IRIS), such as elevated intracranial pressure (ICP).

Opportunistic Infection	Cd4 count	Initiation of ARV	Comments
			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.
Salmonella	Any	As soon as possible or within 2 weeks	The limitation of starting ART is relevant only in terms of a patient's ability to ingest and absorb the drugs (ART). The presence of an enteric infection should not delay ART initiation
MAC	Any	As soon as possible	

* 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

PRINCIPLES OF SELECTING ART FOR 1ST LINE REGIMENS

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

- Co-morbid and organ dysfunction (e.g. renal insufficiency, anemia, psychiatric conditions, heart disease, TB)
- Patients undergoing treatment for an active opportunistic infection (drug-drug interactions)
- Co-infections in particularly with Hepatitis B
- Pregnancy and in women who wish to conceive
- Patient who becomes positive during PrEP.
- Impact of regimen itself e.g. pill burden, pill size, potential for drug interactions, anticipated side effects, food/ fasting requirements, swallowing difficulty, adolescent)
- Baseline drug resistance testing whenever available

An antiretroviral (ARV) regimen for a treatment-naive patient generally consists of;[1-4]

Two nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) in combination with/PLUS a third active ARV drug from ONE of three drug classes:

- a non-nucleoside reverse transcriptase inhibitor (NNRTI)
- an integrase strand transfer inhibitor (INSTI)
- protease inhibitor (PI) with a pharmacokinetic (PK) booster (ritonavir)

5.1 Preferred and Alternative Options for First Line ART

Table 5.1 • Preferred and Alternative ARV Options for patients who are ARV naive

NRTI Backbone		NNRTI		INSTI		Protease Inhibitor (PI)****
(Preferred) TDF/FTC TDF + 3TC TAF/FTC**	PLUS	(Preferred) EFV 400/600	OR	(Preferred) DTG	OR	Special Situation ATV/r
(Alternative) AZT# + 3TC ABC* + 3TC		(Alternative) NVP RPV***		(Alternative) RAL		

* Perform HLA-B*5701 testing before initiating ABC; if result is positive, do not start ABC and add ABC to allergy list. If using ABC/3TC in a patient with HIV VL>100,000 copies/ml, combination with DTG is preferred over NNRTI

\# AZT should not be initiated in patients with baseline Hb < 8.0g/dl.

** TAF regime is preferred over TDF in renal impairment and bone disease.

*** RPV as an alternative when intolerant to EFV/DTG, with VL<100,000 copies/ml.

**** This should only be chosen in special situations and should be discussed with an ID Physician.

5.2 Considerations Prior to Starting Treatment

The choice between an INSTI, PI, or NNRTI as the third drug in an initial ARV regimen should be guided by the regimen's efficacy, barrier to resistance, adverse effects profile, convenience, comorbidities, concomitant medications, the potential for drug-drug interactions and the availability.

5.2.1 Nucleoside and Nucleotide Reverse Transcriptase Inhibitors (NRTI)

FDA-approved NRTIs include ABC, TDF, TAF, ZDV, 3TC, and FTC.

TDF and AZT are generally comparable in terms of efficacy; however, some studies have shown better efficacy and less side effects with TDF-based therapy compared to AZT.

TAF and TDF are two approved forms of tenofovir and can both be used in patients with Hepatitis B coinfection. TDF has been associated with bone and kidney toxicities (should be avoided in patients with chronic kidney disease with CrCl <50ml/min), especially when used with Ritonavir.[5,6] TAF is a prodrug of tenofovir that yields relatively lower plasma levels and high intracellular levels of tenofovir and is less likely to cause kidney and bone toxicities than TDF. However TAF should not be coadministered with rifamycins as it would reduce the drug levels. Conversely, levels of fasting low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides increased more in the TAF group than in the TDF group with no change in total cholesterol to HDL ratio.

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 unless 3rd agent is DTG/PI.[7-10] It is contraindicated if HLA-B*5701 positive as it poses a risk of hypersensitivity. Besides, ABC need to be used with caution in persons with high CVD risk.

5.2.2 Non-Nucleoside Reverse Transcriptase Inhibitors (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. In case of severe hepatotoxicity or skin reactions, NVP should be permanently discontinued. NVP must be avoided in women with CD4 count >250 cells/mm^3 and men with baseline CD4 count >400 cells/mm^3 due to significant increase in incidence of symptomatic hepatic events. Lead in dosing of 2 weeks for NVP should be practiced 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. EFV should be avoided in patients with severe psychiatric illness and in those whose daily functional status is affected by its side effects.

In the ENCORE 1, EFV 400mg daily was found to be better tolerated than standard dose of EFV 600mg daily.[11] Regimens containing EFV 400mg were comparable to EFV 600mg in terms of viral suppression and mortality. EFV 400mg can be co-administered with rifampicin- containing anti-TB treatment, with co-administration well tolerated and plasma concentrations maintained above the levels considered to be effective.

NNRTI has low genetic barrier to resistance with long half-lives. Abrupt discontinuation of NNRTI without maintaining NRTIs backbone will increase the risk of NNRTI resistance due to its long half-life. Hence, when NNRTI is stopped due to adverse event, the backbone NRTIs

should be continued for at least 1 week before stopping all drugs. However, therapeutic plasma concentration of NVP and EFV has been shown to persist for at least 2-3 weeks in some studies, thus it is recommended to consult an infectious diseases physician if the patient cannot be restarted on an alternative regime in the near future.

Rilpivirine

Rilpivirine is recommended in individuals who have baseline viral load of less than 100,000 copies/ml[12,13]. When compared with efavirenz 600mg, in patients with VL<100,000 copies/ml, rilpivirine showed superior virological suppression, with a more tolerable side effect profile. In addition it needs to be taken with food and has significant interactions with acid reducing agents; PPI are contraindicated.

5.2.3 INSTI and PI/r

Integrase strand transfer inhibitors (INSTI) has emerged as a recommended first line regimen (in combination with 2 NRTIs) for most people with HIV infection due to higher rates of viral suppression, favourable adverse effects profile and the tolerability of the medication.

Dolutegravir[14-16]

Advantages

1. Higher and more rapid rates of viral suppression
2. Lower potential for drug-drug interaction
3. Higher genetic barrier for HIV drug resistance

The risk of neural tube defects associated with using DTG at conception has declined since the initial report released in May 2018. As more data has been added to the Tsepamo Cohort, the difference in DTG vs non DTG regimens regarding risk of neural tube defects (NTD) is now no longer statistically significant.[17] This also has been reported similarly by smaller cohorts and have not found any increase in NTD when initiated at the time of conception[18,19]. The risk–benefit models suggest that the benefits of DTG for women of childbearing potential newly initiating ART, which include greater maternal viral suppression, fewer maternal deaths, fewer sexual transmissions and fewer mother-to-child transmissions, are likely to outweigh the risks.

Raltegravir[20,21]

It is the first INSTI approved for use in both treatment naïve and treatment experienced patients. It has a relatively low barrier to resistance. The efficacy and tolerability of raltegravir in combination with two NRTIs was shown in clinical trials. RAL can be given as RAL 400 mg bid or RAL 1200 mg daily (two, 600 mg tablets, if available) in combination with 2 active NRTIs in the treatment naïve patients.

Protease Inhibitors

PI such as Atazanavir/r may be considered as the third agent in a first line ART regime if the patient has the following clinical scenarios:

- Unable to tolerate the side effects of integrase inhibitors / NNRTI
- Baseline resistant testing indicating a resistance to standard first line agent

It is recommended to discuss these patients with infectious disease physician.

Table 5.2 • Special Considerations When Initiating ART

Patient or Regimen Characteristic	Clinical Scenario	Considerations	Rationale/Comments
Pre- ART Characteristic	CD4 cell count <200 cells/ mm^3	**Avoid the following regimens:** RPV- based regimens	Higher rate of virologic failure has been observed.
	HIV VL >100,000 copies/mL	**Avoid the following regimens:** RPV- based regimens ABC/ 3TC with EFV or ATV/r	Higher rate of virologic failure has been observed.
	HLA-B*5701 positive	**Do not use ABC** - containing regimens.	ABC hypersensitivity, a potentially fatal reaction, is highly associated with the presence of the HLA-B*5701 allele.
Presence of Coinfections	HBV infection	Use TDF or TAF, with FTC or 3TC, whenever possible.	TDF, TAF, FTC and 3TC are active against both HIV and HBV. 3TC or FTC associated HBV mutations can emerge rapidly when these drugs used without another drug that is active against HBV.
	Treating TB with rifampicin	TAF is **not recommended** with any rifampicin-containing regimen. If rifampicin is used: **The following are not recommended:** PI, RPV *EFV can be used at a dose of 400mg with anti-tuberculosis therapy as the plasma levels were shown to be maintained above the levels considered to be effective. If RAL is used, increase the dose to 800 mg BD. Do not use once daily RAL. Use DTG at 50 mg BD.	Rifamycin may significantly reduce TAF exposures. Rifampicin is a strong inducer of CYP3A4 and UGT1A1 enzymes, causing significant decrease in concentrations of PIs, INSTIs and RPV. Rifampicin has a less significant effect on EFV. Rifampicin will significantly reduce dolutegravir/raltegravir or PI levels. If patient needs to start on PI or dolutegravir, there need to be a 2-week washout period after discontinuing Rifampicin before the ART can be commenced. If used together, the dose of integrase inhibitor needs to be doubled. Use of rifampicin and PI are not recommended.

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CHAPTER 6

MANAGEMENT OF TREATMENT FAILURE

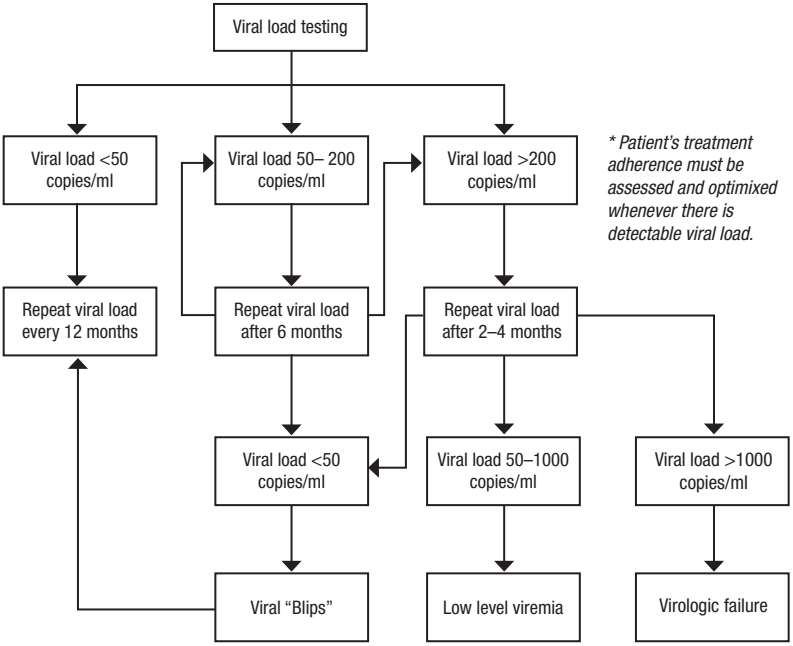
HIV replication is associated with a high mutation rate as the reverse transcriptase lacks proofreading capacity, leading to errors during replication. When a patient's ART levels is subtherapeutic, there is ongoing viral replication under drug pressure; selection of fit minor variants bearing drug resistance mutations is then possible and these can become dominant, leading to virologic failure. Viral load is recommended as the preferred monitoring approach to diagnose and confirm treatment failure.

6.1 Approach to the Patient with Detectable Viral Load

Viral "Blips"
Defined as isolated transient rises in viral load to above detectable level while on treatment after having achieved prior viral suppression and is followed by re-suppression. The levels generally do not exceed 200 copies/mL. It may reflect technical variations in laboratory assay performance, or biological events associated with viral replication (immunization, other viral infection). Isolated "blips" are not associated with subsequent virologic failure.

Low Level Viremia (LLV)
Defined as persistently low, but detectable viral load in the range of 50-1000 copies/mL. The threshold at which LLV becomes predictive of disease progression varies between studies, although evidence shows that incomplete viral suppression leads to the accumulation of resistance mutations with a concomitant increase in viral replication, reduction in CD4 cell counts, increased risk of virologic progression, and clinical deterioration. Furthermore, with increasing resistance, future treatment options are compromised. Patients with LLV should be regularly reinforced on treatment adherence and monitored closely with 2-4 monthly viral loads. Any signs of HIV disease progression or immunological failure should prompt clinician to switch patient to second line therapy.

Virologic Failure
The optimal threshold for defining viral failure and for switching ART regimens has not been established. WHO defines virologic failure by a persistently detectable viral load exceeding 1000 copies/mL (that is, two consecutive viral load measurements within 3-month interval with adherence support between measurements) after at least 6 months of starting a new ART regimen.



6.2 Risk Factors for Treatment Failure

Viral Factors	• Higher baseline HIV RNA level • Lower pre-treatment or nadir CD4 T-cell count • Prior AIDS diagnosis • Presence of drug-resistant virus at baseline • Prior treatment failure, with development of drug resistance or cross resistance
Drug Related Factors	• Previous ARV history using less potent regimens • Drug side effects and toxicity • Suboptimal pharmacokinetics (variable absorption, metabolism, food/fasting requirements, adverse drug-drug interactions with concomitant medications)
Patient Factors	• Co-morbidities (e.g. depression, active substance use) • Incomplete medication adherence and missed clinic appointments
Programme Factors	• Drug supply factors • Retention of patient to treatment programme

6.3 Assessment of Treatment Failure

Treatment failure should be addressed promptly because of the increased risk for HIV disease progression. Assessment of a patient with suspected or confirmed virologic failure should include:

1. ART history
2. Trends in HIV viral load and CD4 counts
3. Occurrence of HIV-related clinical events
4. Physical examination to assess for signs of clinical progression.
5. Results of prior resistance testing (if available)
6. Factors potentially contributing to reduced plasma drug levels such as:
    a) Poor 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)
    b) Incorrect dosing / frequency
    c) Drug intolerance–management strategies include:
        i. Using symptomatic treatment (e.g., antiemetics, antidiarrheals)
        ii. 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)
        iii. changing drug classes (e.g. from an NNRTI to a INSTI / PI if necessary)
    d) Pharmacokinetics
        i. Food/fasting requirements
        ii. Adverse drug-drug interactions with concomitant medications
    e) Co-morbidities

6.4 Viral Resistance Testing

Genotypic, rather than phenotypic, testing is the preferred resistance testing to detect the presence of drug resistance mutations in relevant viral genes. The result is useful in guiding ART regimen selection. In the management of virologic failure, viral resistance testing is recommended.

Viral resistance testing should only be done when viral load is more than 1000 copies/ml and the results must be interpreted in the context of the patient's treatment history. Resistance testing in the setting of virologic failure should be performed while the patient is taking ART or, if that is not possible, within 4 weeks after discontinuing therapy. If more than 4 weeks have elapsed since the ART was discontinued, previously selected resistance mutations can be missed by viral resistance testing due to lack of drug-selective pressure

Table 6.1 • Recommended Second Line Regime

Failing First Line Regimen	Preferred Second Line Regimen	Alternative Second Line Regimens
TDF + FTC (or 3TC) + EFV (or NVP) ABC + 3TC + EFV (or NVP)	TDF + FTC (or 3TC) + DTG[#]	AZT + 3TC + DTG AZT + 3TC + LPV/r (or ATV/r or DRV/r) TDF + FTC (or 3TC) + DRV/r[#]
AZT + 3TC + EFV (or NVP)	TDF + FTC (or 3TC) + DTG ABC + 3TC + DTG	TDF + FTC (or 3TC) + LPV/r (or ATV/r or DRV/r) ABC + 3TC + LPV/r (or ATV/r or DRV/r)
TDF + FTC (or 3TC) + DTG (or RAL) ABC + 3TC + DTG (or RAL)	AZT + 3TC + LPV/r	AZT + 3TC + DRV/r (or ATV/r)
AZT + 3TC + DTG (or RAL)	TDF + FTC (or 3TC) + LPV/r ABC + 3TC + LPV/r	TDF + FTC (or 3TC) + DRV/r (or ATV/r) ABC + 3TC + DRV/r (or ATV/r)

[#] Based on evidence from the NADIA trial.

6.5 Dolutegravir in Second Line Therapy

The WHO recommends dolutegravir over a boosted protease inhibitor for second line therapy. The DAWNING study showed superiority of dolutegravir over ritonavir-boosted lopinavir in second line treatment. As the participants in DAWNING were screened for drug resistance at enrolment and were only recruited to the study if their HIV was sensitive to at least one NRTI, there was a previous concern about switching to dolutegravir-based second line therapy without an active NRTI.

The NADIA trial evaluated options for second line therapy in patients failing on a NNRTI and tenofovir-based first line regimen. The trial not only demonstrated non-inferiority of dolutegravir to boosted darunavir, but also showed that maintaining tenofovir in second line therapy was superior to switching to zidovudine for the outcome of viral suppression. Based on this evidence, we recommend that patients who are failing on a tenofovir-based first line therapy can recycle tenofovir in second line therapy regimen with addition of dolutegravir. In view of the findings in the NADIA trial, switching to second line therapy without consideration of NRTI resistance mutations accumulated during previous treatment failure, or in the absence of viral resistance test, is safe.

In patients taking rifampicin-based TB treatment, dolutegravir should be taken at 50mg twice daily due to the significant reduction of dolutegravir plasma concentration by rifampicin.

Previously there was a concern from an interim analysis of a Botswana surveillance study that showed an increase in neural tube defects in children born to women taking dolutegravir

compared with other antiretrovirals. However, final data from the study revealed a substantially smaller risk difference. Considering the benefit significantly outweighs the risk, we recommend dolutegravir as an option for second line therapy in women who are pregnant or with childbearing potential.

6.6 First-Line Treatment Failure with No Resistance

Following the development of virologic failure with no resistance mutations detected in viral resistance testing, restarting or continuing the previous failing regimen is a reasonable option, especially where poor adherence has been identified as the likely cause and has been addressed. However, the patient should be monitored carefully and repeat viral load after approximately 2-4 months. If there is inadequate virological response, resistance testing should be performed to detect any archived resistance.

6.7 Treatment-Experienced Patients with Limited or No Therapeutic Option

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. Continuing the failing ART regime rather than stopping has been shown to be beneficial provided that the patient has not developed any side effects and is clinically well. This has to be balanced with the fact that there is accumulation of mutations in the long term which may negatively impact future treatment options should they become available. Hence if a potentially viable ART regime becomes available, it must be commenced as soon as possible.

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CHAPTER 7

PREVENTION OF MOTHER-TO-CHILD TRANSMISSION

Antenatal combination antiretroviral therapy (ART) is the recommended method for prevention of maternal-to-child transmission (PMTCT)[1]. Achieving HIV viral load suppression by the third trimester reduces the risk of transmission to 0 to <0.5% (EACS 2018).

Women who present after the second or third trimester must commence ART without delay. An 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 integrase inhibitors for eg. Raltegravir / Dolutegravir 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.

7.1 Pregnant Women Who are ART Naïve

Lifelong ART should be started immediately for all ART Naïve HIV-positive patients including those who are pregnant, regardless of CD4 count. Women should be counselled regarding the benefits of ART in prolonging life expectancy and reducing serious AIDS and non-AIDS events, and that ART should be continued lifelong, even after delivery. Their viral load should be monitored at 2-3 months after commencement of ART and at 32-36 weeks of gestation to determine mode of delivery. If viral load is detectable at 2-3 months after initiation, then to refer to ID for further management.

7.2 Women Who are Stable on ART before Pregnancy

In general, the existing ART is to be continued throughout pregnancy and after delivery, unless taking a regimen that is contraindicated in pregnancy (eg. Tenofovir Alafenamide)[4]. Consultation with an ID physician is strongly recommended if the current regimen is contraindicated in pregnancy and if the patient is experiencing virological failure. Special effort must be made to determine the current CD4 and viral load during the early stages of pregnancy, preferably the first trimester.

7.3 ART Used for PMTCT[4,5]

ART used during pregnancy must consist of 2 NRTIs plus either a NNRTI or a boosted PI or integrase inhibitors. The choice of agents is listed in Table 7.1.

In 2018, initial observations from the Tsepamo observational cohort identified an association between dolutegravir and an increased risk of neural tube defects (NTD) among infants born to women who had been taking it from conception. However, updated data from the study, presented in July of 2021 at the International AIDS Society Conference, showed that the prevalence of NTD was not significantly different from those on non-Dolutegravir based regimens. This was further supported by the DOLOMITE-NEAT ID Network study presented at the AIDS 2022 conference which showed no significant difference in frequency of NTD in infants born to women who had been taking Dolutegravir in the first trimester and second and third trimester. Dolutegravir still remains the drug of choice for first-line therapy by the World Health Organisation even in pregnant women based on a statement issued in July 2019.

Table 7.1 • Choice of ART Combinations

Preferred	Alternative
TDF+FTC+EFV TDF+FTC+RAL* TDF+FTC+DTG*	AZT[#] + 3TC + EFV[a] AZT[#] + 3TC + NVP[b] TDF + FTC + NVP[b] TDF + FTC + LPV/RTV
*Preferred regimen for late presentation at >28 weeks	[#]For close monitoring of Hb if on AZT

[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[6].

[b] NVP should be used with caution in women with CD4 > 250 cells/uL because of possible increased risk of hepatotoxicity and rash[7].

7.4 Mode of Delivery

Women who have received ART before pregnancy or antenatally and have achieved maximal viral load suppression, have a choice between Pre-labour Elective Caesarean Section (PLCS) or spontaneous vaginal delivery (SVD). There is no additional advantage of PLCS over SVD in terms of reduction of transmission in this group[8].

In women who had not achieved maximal viral load suppression, PLCS has been proven to further reduce the risk of transmission[9,10]. The decision between performing PLCS or allowing SVD is based on the viral load at 32–36 weeks of gestation and whether the mother has received any ART in the pre-pregnancy or antenatal period. PLCS should be undertaken at between 38- and 39-weeks gestation.

Table 7.2 • Mode of Delivery According to Viral Load Quantification

Viral Load at 32–36 weeks	Mode of Delivery
< 50 copies/mL	SVD
50–399 copies/mL	*PLCS recommended
> 400 copies/mL	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.

7.5 Intrapartum Intravenous Zidovudine Infusion

Intrapartum IV Zidovudine (AZT) infusion (2 mg/kg for the 1st hour followed by 1 mg/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. For PLCS, Intrapartum IV Zidovudine (AZT) should be started 3 hours before surgery[4]. 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[11].

7.6 Women Presenting in Labour with No Prior ART Exposure

Intravenous (IV) AZT should be given immediately in a woman who is diagnosed with HIV infection presenting in labour and has not received prior ART.

ART should be commenced immediately with fixed-dose AZT and 3TC with Raltegravir/Dolutegravir as the preferred 3rd agent because it rapidly crosses the placenta. If Raltegravir/Dolutegravir is not available, NVP or EFV should be used. After delivery, the ART can be switched

to the 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[12,13]. 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.

7.7 Women Presenting with Spontaneous Rupture of Membrane (ROM)

The decision for the mode of delivery must consider 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[10]. Chorioamnionitis, a potential complication of prolonged ROM has also been associated with perinatal transmission of HIV[14]. Therefore, delivery should be expedited for women with pre-labour ROM at term, either with induction of labour or Caesarean section depending on the obstetrical indication. 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 Preterm 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.

7.8 Breast-Feeding

Breast-feeding is not recommended as it is associated with risk of transmission up to 14% in those who are not virally suppressed[4,13]. This risk reduces to 1% if the woman is virally suppressed. However, breast-feeding is still not encouraged in our population. 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 of ARVs are a major reason for switching or discontinuation of therapy and poor adherence/non-adherence towards ARVs. Differentiating between antiretroviral-related toxicities and disease complications can be difficult.

Active surveillance for clinical signs and symptoms of adverse events is vital during commencement of ART and during subsequent follow-ups to ensure the events are anticipated and managed.

Principles of Managing Adverse Events

1. Identify the adverse event and assess its possible cause: ARVs, 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 ARV (except for NVP-induced rash / hepatotoxicity). Implement symptomatic therapy. Counsel and monitor patients, emphasize the importance of adherence despite toxicity.
4. Moderate or severe toxicities may require substitution of the drug with another drug of the same ARVs class, but with a different toxicity profile.
5. Severe life-threatening toxicity requires discontinuation of ALL ARVs until the patient is stabilised 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 ARV, all ARVs must be stopped together. Stopping only one drug can lead to resistance. For stopping regimes with NNRTIs, refer to 'Stopping / Interrupting NNRTIs'.

Table 8.1 • NRTIs & NNRTIs Substitutions for Toxicity and Intolerance

ARV	Adverse Events	Risk Factors/Comments	Suggested Management
ABC	Hypersensitivity reactions	• Presence of HLA-B*5701 gene (test available in selected labs) indicates higher risk of experiencing hypersensitivity reactions	Substitute with TDF, TAF or ZDV (do not re-challenge)
	Cardiovascular events (MI, ischaemic stroke)	• Several observational studies linked ABC use with CV disease and cardiac events	• Substitute with TDF, TAF or ZDV
TDF	Renal tubular toxicity (proximal renal tubulopathy) Fanconi syndrome	• Underlying chronic kidney disease. • Avoid if eGFR <50mL/min • Older age • BMI <18.5 (or bodyweight >50kg)	• Substitute with ABC or TAF • Switching from TDF to TAF is associated with improvement in proteinuria and renal biomarkers

ARV	Adverse Events	Risk Factors/Comments	Suggested Management
TDF		• Underlying diabetes mellitus & uncontrolled hypertension • Concomitant use of nephrotoxic drugs or a boosted PI	
	Bone density reduction	• History of osteomalacia and mineral density fracture • At risk of osteoporosis /bone loss	• Substitute with ABC or TAF (TAF associated with smaller decline in BMD compared to TDF)
	Hepatic flares	• When TDF discontinued in patients with severe exacerbations of HBV or HBV resistance develops	• Use alternative drug for Hep. B (e.g., entecavir)
ZDV	Bone marrow suppression (anaemia, neutropaenia) Myopathy Lipodystrophy (rare)	• Baseline anaemia/ neutropaenia • CD4 count ≤ 200 cells/mm^3	• Substitute with TDF, TAF or ABC
EFV RPV	CNS/neuropsychiatric side effects (hallucinations, psychosis, depression, suicidal ideation)	• History of psychiatric illness • Monitor for depression; prolonged or severe depression should prompt a change in regime, especially if the patient has other risk factors for depression. • Concomitant use of substance with neuropsychiatric effects • Genetic factor resulting in high serum EFV concentration • Increased absorption of EFV with food	• Substitute with NVP • Substitute with ETR or PI or INSTI (but INSTI a/w insomnia, extra monitoring is required) • If keen to continue in mild depression, closely monitor for deterioration of depression (care takers advised to monitor for deterioration of depression)
	Cardiac (QTc interval Prolongation)	• Pre-existing heart disease and concomitant medications that may cause QT prolongation	• Substitute with INSTI
	Hypersensitivity reactions Rash	• Lesser incidence compared to NVP • Usually occur by 2nd week of therapy • May be accompanied by elevated liver transaminases	• Substitute with any non-NNRTIs • If no systemic manifestations occur, continuation of therapy is indicated with antihistamines for symptomatic control
NVP	Hepatitis Hypersensitivity reactions Rash	• Females with baseline CD4 >250 cells /mm^3 • Males with baseline CD4 >400 cells/mm^3	• Substitute with EFV, INSTI or PI based regime

Table 8.2 • Adverse Events of Antiretroviral Drugs

ARV	Comments	Management
Bone Marrow Suppression		
ZDV	• Incidence: (anemia) adult 1%, pediatric 23%; (leukopenia) 39% • Avoid concurrent bone marrow suppressants • Monitor FBC with differential at weeks 4, 8, 12 (more frequently in patients at risk)	• Discontinue ZDV if Hb has dropped ≥ 25% of baseline / < 8.0 g/dL OR • When patient develops symptomatic anemia and / or leukopenia • If Hb is dropping and ZDV is continued, closely monitor Hb and advice patient on symptoms of anemia.
Central Nervous System Effects		
EFV **RPV**	• Neuropsychiatric Events: EFV > RPV • EFV: Incidence: 40%; only 3% severe enough to justify discontinuation of EFV. • Symptoms include: – Vivid / abnormal dreams – Feeling off balance – Feels like falling over – Feels like the room is spinning – Unsteady walk – Feels like body is spinning – Feels light-headed – Feels hangover • Insomnia, mood fluctuations, depression, depersonalization, paranoid delusions, confusion, and even suicidal ideation may occur. Potential additive effect with alcohol and other psychoactive drugs. False positive cannabinoid and benzodiazepine urine test. • RPV: Depression, headache, sleep disturbances	• Symptoms improve with continuation of EFV-based regimen. 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 restarting ARV drugs yet.
Gastrointestinal Intolerance		
All ARVs, **Especially : Protease inhibitors (PIs)** **LPV/r** **ZDV** **EFV**	• Symptoms include abdominal discomfort, loss of appetite, nausea, vomiting, heartburn, abdominal pain, constipation. • Nausea is common with ZDV (vomiting, 6-25%), more than other NRTIs. Occurs in 2-12% of EFV usage. • Diarrhoea 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 causes.	• Rule out other causes such as pancreatitis or acute gastroenteritis • Symptoms may spontaneously resolve or become tolerable with time. • Nausea and vomiting: – Antiemetic prior to dosing – Switch to less emetogenic ARV if persistent vomiting • Diarrhea: – Antimotility agents (e.g. loperamide, diphenoxylate/ atropine) – Monitor pancreatic enzymes • Severe GI symptoms: – Rehydration and electrolyte replacement as indicated

Hepatotoxicity		
ARV	**Comments**	**Management**
All NNRTIs **All PIs** **Most NRTIs**	**NNRTIs** **NVP** • Usually occurs in the first 2-3 months of treatment. Dose escalation during initiation of therapy reduces the risk of elevated liver enzymes which are often associated with rash/hypersensitivity. • Higher risk of NVP-associated hepatotoxicity in ARV-naïve females with baseline CD4 >250 cells/uL and males with baseline CD4 >400 cells/uL. **EFV** • Most cases relate to an increase in transaminases • Fulminant hepatitis leading to death or hepatic failure has been reported with EFV-based ART regimen EFV and NVP are not recommended in moderate to severe hepatic impairment (Child-Pugh class B or C) and not to use as part of postexposure prophylaxis **PIs** • Usually occurs after weeks to months of treatment • ATV: Indirect hyperbilirubinemia may occur (35–49%) **NRTIs** • Patients with HBV/HIV coinfection may develop severe hepatic flares with the withdrawal of TAF, TDF, 3TC, FTC or with the emergence of resistance of these drugs especially if the patient is receiving only one anti-HBV agent	**Symptomatic patients:** – Discontinue all ARVs and other potential hepatotoxic agents **Asymptomatic patients:** – If ALT >5–10x ULN, to consider discontinuing ARVs After serum transaminases return to normal, start a new ARV regimen without the potential offending agent(s)
Hyperlipidemia		
All PIs **NNRTIs** **NRTIs**	**PIs** • **All RTV boosted PIs** – ↑ LDL, ↑ HDL and ↑ TG – ↑ TG: LPV/r (3-36%) > DRV/r, ATV/r – Usually seen within 2–3 months of starting PIs. **NNRTIs** • **EFV > NVP** – ↑ LDL, ↑ HDL and ↑ TG – ↑TC by 20–40% – ↑ LDL, ↑ HDL and ↑ TG • ↑ LDL, TC and TG in NNRTIs < PIs **NRTIs** – ZDV > ABC: ↑ LDL and ↑TG – TAF: ↑ LDL, ↑ HDL and ↑ TG, – TDF has been associated with lower lipid levels than ABC or TAF	• Lifestyle modifications (e.g., diet, exercise, smoking cessation) • Consider switching to agents with less propensity for causing hyperlipidemia • Pharmacologic management: – Refer to CPG on Management of Dyslipidemia – Refer to Table 9.1 & 9.2 for drug interactions between ARV and lipid-lowering agents.

Hypersensitivity Reaction (HSR)		
ARV	**Comments**	**Management**
ABC **NNRTIs** **INSTIs**	**ABC** • Contraindicated if patient is tested positive for HLA-B*5701 • Incidence: Up to 8% • Median onset is 9 days; approximately 90% of reactions occur within the first 6 weeks • Symptoms include: – (In descending frequency): fever, skin rash, malaise, nausea, headache, myalgia, chills, diarrhea, vomiting, abdominal pain, dyspnea, arthralgia, and respiratory symptoms. – The continuation of ABC in hypersensitive patients migh precipitate a life-threatening reaction such as hypotension and respiratory distress. **NNRTIs** • **NVP** – HSR of hepatotoxicity and rash that may be accompanied by fever, general malaise, fatigue, myalgias, arthralgias, blisters, oral lesions, conjunctivitis, facial oedema, eosinophilia, renal dysfunction, granulocytopenia, or lymphadenopathy. – Higher risk in ARV-naïve females with baseline CD4 >250 cells/uL and males with baseline CD4 >400 cells/uL. • Also, can occur with EFV and RPV **INSTIs** • **RAL** – HSR reported when given concomitantly with other drugs associated with HSRs. • **DTG** – Reported <1% in clinical trials. May be accompanied by elevated liver transaminases.	**ABC** • Discontinue ABC and switch to another NRTI • Rule out other causes of symptoms (e.g., intercurrent illnesses such as viral syndromes and other causes of skin rash) • Signs and symptoms usually resolve 48 hours after discontinuation of ABC • Manage with symptomatic support (antipyretic, fluid resuscitation, pressure support if necessary) • Do not rechallenge patients with ABC if HSR suspected regardless of the HLA-B*5701 status **NNRTIs** • Dose escalation during initiation of NYP therapy reduces the risk. • Consider switching to non-NNRTI ART **INSTIs** • All ARVs should be stopped if HSR occurs. • Consider switching to non-INSTI ART
Lactate: Hyperlactatemia / Lactic Acidosis		
ZDV > other NRTIs	• Reported with older NRTIs such as d4T, ZDV, and ddI, but not with ABC, 3TC, FTC, TAF, or TDF. • 3 clinical syndromes: i. Lactic acidosis with hepatic steatosis ii. Symptomatic lactatemia without acidosis / liver failure iii. Asymptomatic lactatemia	• Lactate 2-5 mmol/L but asymptomatic: Observe. • Lactate 2-5mmol/L + symptoms ± liver abnormality: Stop ARVs

Lactate: Hyperlactatemia / Lactic Acidosis (Cont)		
ARV	**Comments**	**Management**
ZDV > other NRTIs	• Symptoms include: – Nonspecific GI prodrome (nausea, anorexia, abdominal pain, vomiting), weight loss, and fatigue – Subsequent symptoms: tachycardia, tachypnea, hyperventilation, jaundice, muscular weakness, mental status changes, or respiratory distress – May present with multi-organ failure (e.g., hepatic failure, acute pancreatitis, encephalopathy, and respiratory failure) – Typically present after several months of therapy – Risk & severity increases with time on treatment (usually takes months/ years) but sometimes can occur soon after starting 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 > 5mmol/L or lactic acidosis: – Stop ARVs – Exclude other precipitating factors – Intensive care support – To consider: IV thiamine and/or riboflavin / bicarbonate infusions / haemodialysis *Note. Do not measure lactate unless symptomatic* • ART options: – 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		
ZDV > other NRTIs	• Lipoatrophy (fat wasting): – Face, arms, leg, buttocks – Associated with history of exposure to d4T or ZDV (d4T > ZDV) – Not reported with ABC, 3TC or FTC, TAF or TDF – More likely when NRTIs combined with EFV than boosted PI • Lipohypertrophy (fat accumulation): – Accumulation of visceral, truncal, dorsocervical, and breast fat – 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.	• Switch from thymidine analogs (d4T or ZDV) to TDF or ABC may slow or halt progression but may not fully reverse effects • There is no clinical evidence that switching to another first line regimen will reverse lipohypertrophy. • Surgical options provide cosmetic improvement: – Lipoatrophy: Facial filling with collagen, synthetic polymers or silicone – Lipodystrophy: Liposuction

Nephrotoxicity / Urolithiasis		
ARV	**Comments**	**Management**
TDF **TAF** **RPV** **ATV LPV/r**	**TDF** • Symptoms include ↑SrCr, proteinuria, hypophosphatemia, urinary phosphate wasting, glycosuria, hypokalemia, normal anion gap metabolic acidosis • Concurrent use with PI: ↑ risk **TAF** • Less impact on renal biomarkers and lower rates of proteinuria than TDF. **RPV** • Inhibits Cr secretion without reducing renal glomerular function. **PIs** • ATV: May cause kidney stone / crystal formation • ATV and LPV/r: Associated with increased risk of chronic kidney disease in a large cohort study	**Prevention** • Drink at least 1.5–2 liters of non-caffeinated fluid per day (preferably water) **Treatment** • Switch to other PIs should be made if ATV is the presumed cause of the calculi • Consider replacing TDF with a non-tenofovir drug or TAF if: – Urine P/C 20-50 mg/mmol – eGFR <60 or eGFR > 60 mL/min, but decrease in eGFR by 5 mL/min per year for at least 3 consecutive years or confirmed 25% eGFR decline from baseline – Co-morbidities with a high risk of CKD (i.e., diabetes and hypertension) – Body weight < 60 kg – Use of boosted PI as a third agent • Refer to Urologists when indicated
Neuromuscular Weakness Syndrome (ascending)		
NRTIs	• It occurs after months of ARVs use • Symptoms: – Rapidly progressive to acute inflammatory demyelinating polyneuropathy, mimicking Guillain-Barré syndrome	• Discontinue ARVs • Supportive care, including mechanical ventilation if needed • 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		
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
Myopathy/Elevated Creatine Phosphokinase		
ZDV **RAL** **DTG**	• ZDV: Myopathy • RAL and DTG: ↑ CPK, rhabdomyolysis, and myopathy or myositis have been reported.	• A switch of regimen should be made if the clinician believes ARV is the cause.

Rash		
ARV	**Comments**	**Management**
NVP **EFV**	• The rash is greatest in the first 6 weeks of treatment (Malaysian data: >20%) • Constitutional symptoms: – Fever> 37ºC – Blistering – Oral lesions – Conjunctivitis – Significant elevations in LFTs – Facial oedema – Myalgia/arthralgia – Generalized malaise • EFV rash is commonly transient & rarely causes serious rash.	**Prevention** • In the presence of mild to moderate rash without constitutional symptoms or biochemical hepatitis, NVP 200mg q24h 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 > 7 days, reintroduce with 200mg q24h*
Stevens-Johnson Syndrome (SJS) / Toxic Epidermal Necrosis (TEN)		
NVP>EFV **Others:** **ABC** **ZDV** **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 EFV • Aggressive symptomatic support

Table 8.3 • ARV Drugs and Common Adverse Events

NRTI	
Drug	**Adverse Events**
ABC	Refer to table 8.1
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 exacerbations may occur in HBV co-infected patientswho discontinue TDF
TAF	• Reduced bone mineral density, osteomalacia • Headache
ZDV	• Bone marrow suppression: macrocytic anaemia or neutropaenia • Gastrointestinal intolerance, headache, insomnia, asthenia • Nail pigmentation • Lactic acidosis with hepatic steatosis (rare but potentially life-threatening toxicity)

NNRT	
Drug	**Adverse Events**
EFV	• Rash • Central nervous system symptoms • Increased transaminase levels • Gynecomastia • False-positive results reported with some cannabinoid and benzodiazepine screening assays
ETV	• Rash
RPV	• Headache, depression, sleep disturbance • Hepatitis • Reduced eGFR due to inhibition of creatinine secretion from proximal renal tubule, but no effect on glomerular filtration • Rash
NVP	• Rash, including Stevens-Johnson syndrome • Symptomatic hepatitis, including fatal hepatic necrosis, has been reported
Protease Inhibitor	
LPV	• Diarrhoea, nausea, vomiting • Prolonged PR interval—first degree symptomatic AV block in some patients • Use with caution in patients with underlying conduction defects or on concomitant medications that can cause PR prolongation • Hyperglycemia / insulin resistance • Lipodystrophy • Hyperlipidemia • Hepatotoxicity
ATZ	• Indirect hyperbilirubinemia • Prolonged PR interval—first degree symptomatic AV block in some patients • Use with caution in patients with underlying conduction defects or on concomitant medications that can cause PR prolongation • Hyperglycemia • Lipodystrophy • Nephrolithiasis • Possible increased bleeding episodes in patients with haemophilia
DRV	• Skin rash (10%)—DRV has a sulfonamide moiety; Stevens-Johnson syndrome and erythrema multiforme have been reported • Hepatotoxicity • Diarrhoea, nausea • Headache • Hyperlipidemia • Increased transaminase levels • Hyperglycemia • Lipodystrophy • Possible increased bleeding episodes in patients with haemophilia

Protease Inhibitor (CONT)	
Drug	**Adverse Events**
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 patients with hemophilia
Integrase Inhibitors	
DTG	• Insomnia, headache • Hepatotoxicity (higher risk in patients with hepatitis B and C coinfection and liver disease) • Rash • Hyperglycemia • Reduced eGFR due to inhibition of creatinine secretion from proximal renal tubule, but no effect on glomerular filtration • Nausea • Hypersensitivity syndrome (<1%)
RAL	• Increased CK; muscle weakness and rhabdomyolysis • Rash (uncommon) • Headache, sleep disturbance • DRESS syndrome (< 2%) • Transaminitis • Nausea

DOSE ADJUSTMENT OF ARVS FOR IMPAIRED RENAL FUNCTION

ARV	CrCl[1](mL/min)				Haemodialysis
	Usual dose	30-49	15-29	< 15	
NRTIs					
ABC	600mg q24h or 300mg q12h	No dose adjustment required			
3TC	300mg q24h	150mg q24h	1 x 150mg, then 100mg q24h, or 150mg q24h[3]	1 x 150mg, then 50mg q24h, or 75mg q24h[3]	1 x 50mg, then 25-50mg q24h, or 75mg q24h[3]
TAF	25mg q24h	No dose adjustment required		Not recommended	25mg q24h[2]
TDF	300mg q24h	300mg q48h	**CrCl 10-29 ml/min:** 300mg q72-96h (if no alternative)	**CrCl <10 ml/min and not on HD:** Not recommended	300mg q7d[2] (if no alternative)
ZDV	300mg q12h	No dose adjustment required		300mg q24h	300mg q24h[2]
ABC/3TC	600/300mg q24h	Use individual drugs for dose adjustment			
ZDV/3TC	300/150mg q12h	Use individual drugs for dose adjustment			
TAF/FTC	25/200mg q24h	No dose adjustment required	Not recommended if not on HD		25/200mg q24h[2]
TDF/FTC	300/200mg q24h	300mg/200mg q48h	Not recommended		
NNRTIs					
EFV	600mg q24h or 400mg q24h	No dose adjustment required			
ETV	200mg q12h	No dose adjustment required			
NVP	200mg q24h for 14 days, then 200mg q12h	No dose adjustment required			
RPV	25mg q24h	No dose adjustment required			
PIS					
ATV/r	300mg/100mg q24h	No dose adjustment required			
DRV/r	800mg/100mg q24h or 600mg/100mg q12h	No dose adjustment required			
LPV/r	400mg/100mg q12h	No dose adjustment required			
INSTIS					
DTG	50mg q24h	No dose adjustment required			
RAL	400mg q12h	No dose adjustment required			

1 CrCl: To use Cockcroft-Gault equation for calculation.
2 On a dialysis day, administer after dialysis.
3 Depending on available tablet strength.

DOSE ADJUSTMENT OF ARVS FOR IMPAIRED HEPATIC FUNCTION

ARV	Dose adjustments
NRTIs	
ABC	Child-Pugh Class A: 200mg q12h (use oral solution) Child-Pugh Class B or C: Contraindicated
FTC	No dose adjustment required
3TC	No dose adjustment required
TAF	Child-Pugh Class B or C: Not recommended
TDF	No dose adjustment required
ZDV	Reduce dose by 50% or double the interval between doses if Child-Pugh Class C
ABC/3TC	Child-Pugh Class A: Use individual drugs for dose adjustment Child-Pugh Class B or C: Contraindicated
ZDV/3TC	Use individual drugs for dose adjustment
TAF/FTC	Use individual drugs for dose adjustment
TDF/FTC	No dose adjustment required
NNRTIs	
EFV	Child-Pugh Class A: No dose adjustment required; use with caution Child-Pugh Class B or C: Not recommended
ETV	Child-Pugh Class A or B: No dose adjustment required Child-Pugh Class C: No data
NVP	Child-Pugh Class A: No dose adjustment required Child-Pugh Class B or C: Contraindicated
RPV	Child-Pugh Class A or B: No dose adjustment required Child-Pugh Class C: No data
PIs	
ATV	Child-Pugh Class A: No dose adjustment required Child-Pugh Class B: 300mg q24h (unboosted) for ARV-naïve patients only Child-Pugh Class C: Not recommended
DRV	Child-Pugh Class A or B: No dose adjustment required Child-Pugh Class C: Not recommended
LPV/r	No dose adjustment recommendation; use with caution
RTV	Refer to recommendations for the primary PI
INSTIs	
DTG	Child-Pugh Class A or B: No dose adjustment required Child-Pugh Class C: Not recommended
RAL	Child-Pugh Class A or B: No dose adjustment required Child-Pugh Class C: No data
TAF/FTC/BIC	Child-Pugh Class A or B: No dose adjustment required Child-Pugh Class C: No data/Not recommended

COMMON ARV-DRUG INTERACTIONS

Drug-drug interactions with ARV are unfortunately common and can be devastating. It is important that all interactions are checked before anything is started.

Common drug-drug interactions are listed in the tables below (Table 10.1, Table 10.2, Table 10.3 and Table 10.4).

An easier option would be to use a HIV drug interaction checker application for smartphones or via websites. The most used is the "HIV iChart" application by the University of Liverpool or available at URL www.hiv-druginteractions.org

Table 10.1 • Common NRTIs Drug Interactions

Concomitant Drug Class	NRTI	Description of Interaction	Suggested Management
Antiviral			
Adefovir	TDF TAF	No data	Avoid co-administration May increase serum concentrations of TDF and/or other renally eliminated drugs Potential increase in hematologic toxicities
	ZDV	No significant effect	
Ganciclovir Valganciclovir	TDF TAF	No data	May increase serum concentrations of tenofovir and/or ganciclovir Monitor for dose-related toxicities
Ribavirin	TDF	With Sofosbuvir 400mg: ←→ Tenofovir AUC	No dose adjustment necessary
	ZDV	Ribavirin inhibits phosphorylation of ZDV.	Avoid coadministration if possible or closely monitor HIV virologic response and possible hematologic toxicities
INSTI			
DTG	TAF	←→ TAF AUC	No dose adjustment necessary
	TDF	←→ TDF AUC ←→ DTG AUC	No dose adjustment necessary
RAL	TDF	RAL AUC ↑ 49%	No dose adjustment necessary
Anticonvulsants			
Carbamazepine	TAF	TAF AUC ↓ 55%	Coadministration is not recommended
Phenobarbital Phenytoin	TAF	TAF AUC ↓ possible	Coadministration is not recommended

Concomitant Drug Class	NRTI	Description of Interaction	Suggested Management
Antimycobacterial			
Rifampicin	**TAF**	TAF AUC ↓ 55%	Use with caution due to limited evidence
	TDF	←→TAF AUC	No dose adjustment necessary
Rifabutin	**TAF**	↓ TAF possible	Coadministration is not recommended
	TDF	←→TAF AUC	No dose adjustment necessary
Narcotics			
Buprenorphine	**3TC** **TDF** **TAF** **ZDV**	No significant effect	No dose adjustment necessary
Methadone	**ABC**	Methadone clearance ↑ 22%	No dose adjustment necessary
	ZDV	ZDV AUC ↑ 29%–43%	Monitor for ZDV related adverse effects
PI			
LPV/r	**TAF**	TAF AUC ↑ 47%	No dose adjustment necessary
	TDF	TDF AUC ↑ 32% ←→ LPV/r AUC	Clinical significance unknown Monitor for TDF- associated toxicity
DRV/r	**TAF**	←→TAF AUC	No dose adjustment necessary
	TDF	TDF AUC ↑ 22%	Clinical significance unknown Monitor for TDF- associated toxicity
ATV **ATV/r**	**TAF**	With ATV/r: TAF AUC ↑ 91%	No dose adjustment necessary
	TDF	With unboosted ATV: ATV AUC ↓ 25%	Do not administer unboosted ATV with TDF
Others			
Allopurinol	**ZDV**	ZDV AUC ↑ 31%	Monitor for ZDV-related adverse effects
St. John's Wort	**TAF**	↓ TAF possible	Avoid co-administration

Table 10.1 • Common NNRTIs Drug Interactions

Concomitant Drug Class	NNRTI	Description of Interaction	Suggested Management
Antiviral			
Antacids	**RPV**	↓ RPV expected when given simultaneously	Give antacids at least 2 hours before or at least 4 hours after RPV
H2RA	**RPV**	↓ RPV	Give H2RA at least 12 hours before or at least 4 hours after RPV
PPI	**RPV**	With Omeprazole 20mg/day: RPV AUC ↓ 40% and Cmin ↓ 33%	Contraindicated Avoid co-administration
Antibiotics			
Clarithromycin	**EFV** **ETR** **RPV** **NVP**	Clarithromycin AUC ↓ ↑ NNRTI AUC	Consider alternative agent, such as azithromycin, for MAC prophylaxis and treatment
Anticoagulants / Antiplatelets			
Warfarin	**EFV** **ETR** **NVP**	↑ or ↓ warfarin possible	Monitor INR and adjust warfarin dose accordingly
Apixaban **Rivaroxaban**	**EFV** **ETR** **NVP**	↓ apixaban/rivaroxaban possible	Consider alternative therapy
Dabigatran	**All NNRTIs**	←→ dabigatran expected	No dose adjustment necessary
Ticagrelor	**EFV** **ETR** **NVP**	↓ ticagrelor expected	Consider alternative therapy
Anticonvulsants			
Carbamazepine **Phenobarbital** **Phenytoin**	**EFV**	With carbamazepine: CBZ AUC ↓ 27%, EFV AUC↓ 36% With Phenytoin:↓ EFV ↓ Phenytoin possible	Monitor anticonvulsant and EFV levels or, if possible, use alternative anticonvulsant
	ETR	↓ anticonvulsant and ETR possible	Avoid co-administration Consider alternative
	RPV	↓ RPV possible	Contraindicated Avoid co-administration
	NVP	↓ anticonvulsant and NVP possible	Monitor anticonvulsant and NVP levels and virologic responses or consider alternative anticonvulsant.

Concomitant Drug Class	NNRTI	Description of Interaction	Suggested Management
Antidepressants			
Bupropion	**EFV** **NVP**	Bupropion AUC ↓ 55%	Titrate bupropion dose based on clinical response
Escitalopram	**EFV** **ETR** **NVP**	↓ antidepressant possible	Titrate escitalopram dose based on clinical response
Fluoxetine **Fluvoxamine**	**All NNRTIs**	←→ antidepressant expected	No dose adjustment necessary
Paroxetine	**EFV** **ETR**	No significant effect	No dose adjustment necessary
Sertraline	**EFV**	Sertraline AUC ↓ 39%	Titrate sertraline dose based on clinical response
Antifungals			
Fluconazole	**EFV**	No significant effect	No dose adjustment necessary
	ETR	ETR AUC ↑ 86%	No dose adjustment necessary Use with caution
	NVP	NVP AUC ↑ 110%	Increased risk of hepatotoxicity Monitor NVP toxicity or use alternative ARV agent
	RPV	↑ RPV possible	No dose adjustment necessary
Isavuconazole	**EFV** **ETR** **NVP**	↓ isavuconazole possible	Monitor response closely and adjust isavuconazole dose
	RPV	↑ RPV possible	No dose adjustment necessary
Itraconazole	**EFV,** **NVP**	Itraconazole AUC ↓	Avoid this combination if possible. If co-administered, monitor response closely and adjust itraconazole dose
	ETR	↓ itraconazole possible ↑ ETR possible	Monitor response closely and adjust itraconazole dose
	RPV	↑ RPV possible	No dose adjustment necessary Monitor for RPV toxicity
Posaconazole	**EFV**	Posaconazole AUC ↓ 50% ←→ EFV	Avoid concomitant use unless the benefit outweighs the risk. If co-administered, monitor response closely and adjust dose
	RPV	↑ RPV possible	No dose adjustment necessary Monitor for RPV toxicity

Concomitant Drug Class	NNRTI	Description of Interaction	Suggested Management
Anticonvulsants			
Carbamazepine Phenobarbital Phenytoin	**EFV**	With carbamazepine: CBZ AUC ↓27%, EFV AUC↓36% With Phenytoin: ↓EFV ↓ Phenytoin possible	Monitor anticonvulsant and EFV levels or, if possible, use alternative anticonvulsant
	ETR	↓ anticonvulsant and ETR possible	Avoid co-administration Consider alternative
	RPV	↓ RPV possible	Contraindicated Avoid co-administration
	NVP	↓ anticonvulsant and NVP possible	Monitor anticonvulsant and NVP levels and virologic responses or consider alternative anticonvulsant.
Antidepressants			
Bupropion	**EFV** **NVP**	Bupropion AUC↓55%	Titrate bupropion dose based on clinical response
Escitalopram	**EFV** **ETR** **NVP**	↓ antidepressant possible	Titrate escitalopram dose based on clinical response
Fluoxetine **Fluvoxamine**	**All NNRTIs**	←→ antidepressant expected	No dose adjustment necessary
Paroxetine	**EFV** **ETR**	No significant effect	No dose adjustment necessary
Sertraline	**EFV**	Sertraline AUC ↓ 39%	Titrate sertraline dose based on clinical response
Antifungals			
Fluconazole	**EFV**	No significant effect	No dose adjustment necessary
	ETR	ETR AUC ↑ 86%.	No dose adjustment necessary Use with caution
	NVP	NVP AUC ↑ 110%.	Increased risk of hepatotoxicity Monitor NVP toxicity or use alternative ARV agent
	RPV	↑ RPV possible	No dose adjustment necessary
Isavuconazole	**EFV** **ETR** **NVP**	↓ isavuconazole possible	Monitor response closely and adjust isavuconazole dose
	RPV	↑ RPV possible	No dose adjustment necessary

Concomitant Drug Class	NNRTI	Description of Interaction	Suggested Management
Antifungals			
Itraconazole	**EFV, NVP**	Itraconazole AUC↓	Avoid this combination if possible. If co-administered, monitor response closely and adjust itraconazole dose
	ETR	↓ itraconazole possible ←→ ETR possible	Monitor response closely and adjust itraconazole dose
	RPV	↑ RPV possible	No dose adjustment necessary Monitor for RPV toxicity
Posaconazole	**EFV**	Posaconazole AUC↓ 50% ←→ EFV	Avoid concomitant use unless the benefit outweighs the risk. If co-administered, monitor response closely and adjust dose
	RPV	↑ RPV possibl	No dose adjustment necessary Monitor for RPV toxicity
Voriconazole	**EFV**	Voriconazole AUC ↓77% EFV AUC ↑ 44%	Contraindicated at standard doses Co-administration with dose adjustment: Voriconazole 400mg q12h and EFV 300mg q24h
	ETR	←→ Voriconazole AUC ETR AUC ↑ 36%	No dose adjustment necessary
	RPV	↑ RPV possible	No dose adjustment necessary
	NVP	↓ Voriconazole possible ↑ NVP possible	Monitor for toxicity and antifungal response
Antimalarials			
Artemether/ Lumefantrine	**EFV**	Artemether AUC ↓ 79% DHA AUC ↓ 75% Lumefantrine AUC ↓ 56%	Consider alternative If used in combination, monitor closely for antimalarial efficacy
	ETR	Artemether AUC ↓ 38% ←→ DHA AUC ←→ Lumefantrine AUC ←→ ETR AUC	Consider alternative If used in combination, monitor closely for antimalarial efficacy
	NVP	Artemether AUC ↓ 67% to 72% DHA & Lumefantrine: Study results are conflicting	Consider alternative If used in combination, monitor closely for antimalarial efficacy and lumefantrine toxicity

Concomitant Drug Class	NNRTI	Description of Interaction	Suggested Management
Antimycobacterial			
Rifampin	EFV	EFV AUC ↓ 26%	No dose adjustment necessary
	ETR NVP	Significant ↓ ETR possible NVP ↓ 20% to 58%	Avoid co-administration
	RPV	RPV AUC ↓ 80%	Contraindicated
Rifabutin	EFV	Rifabutin ↓ 38%	Rifabutin dose: 450–600 mg/day
	ETR	←→ Rifabutin and metabolite AUC ETR AUC ↓ 37%	Do not co-administer ETR plus PI/r with rifabutin Use rifabutin 300 mg/day
	RPV	Rifabutin plus RPV 50mg OD vs RPV 25mg OD alone: ←→ RPV AUC and Cmin	Increase RPV dose to 50mg OD No dose adjustment for rifabutin
	NVP	Rifabutin AUC ↑ 17% and metabolite AUC ↑ 24% NVP Cmin ↓ 16	No dose adjustment necessary Use with caution.
Antipsychotic			
Aripiprazole	EFV ETR NVP	↓ aripiprazole expected	Monitor effectiveness of antipsychotic. Consider doubling usual dose of aripiprazole over 1–2 weeks Refer to aripiprazole prescribing information for dosing recommendations
Benzodiazepines			
Alprazolam	EFV, ETR NVP	↓ alprazolam possible	Monitor for therapeutic effectiveness of alprazolam
Diazepam	EFV NVP	↓ diazepam possible	Monitor for therapeutic effectiveness of diazepam
	ETR	↑ diazepam possible	Decreased dose of diazepam may be necessary Monitor for diazepam toxicity
Lorazepam	EFV ETR NVP	←→ lorazepam expected	No dose adjustment necessary
Midazolam	EFV	↑ or ↓ midazolam possible	Monitor therapeutic effectiveness and toxicity of midazolam
	ETR	Midazolam AUC ↓ 31% Midazolam active metabolite Cmax ↑ 57%	Monitor therapeutic effectiveness of midazolam
	NVP	↓ midazolam possible	Monitor therapeutic effectiveness of midazolam

Concomitant Drug Class	NNRTI	Description of Interaction	Suggested Management
Cardiac Medications			
CCBs (Dihydropyridine and non-dihydropyridine)	**EFV ETR NVP**	↓ CCBs possible	Titrate CCB dose based on clinical response
Corticosteroids			
Dexamethasone	**EFV ETR NVP**	↓ NNRTI 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
Hepatitis C Direct-Acting Antiviral Agents			
Daclatasvir	**EFV ETR NVP**	Daclatasvir 120mg OD plus EFV 600mg ON vs Daclatasvir 60mg alone: Daclatasvir Cmin ↓17%, AUC↑ 37%	The recommended dose is daclatasvir 90mg OD
	RPV	No data	No dose adjustment necessary
Hormonal Therapies			
Contraceptives: Ethinyl estradiol Etonogestrel Levonorgestrel	**EFV**	←→ Ethinyl estradiol Etonogestrel (metabolite of oral desogestrel) Cmin ↓ Levonorgestrel (metabolite of oral norgestimate) AUC ↓	Use alternative or additional contraceptive methods.
HMG-CoA Reductase Inhibitors			
Lovastatin Simvastatin Atorvastatin	**EFV ETR NVP**	Statin AUC ↓	Adjust statin dose according to lipid response, but do not exceed the maximum recommended dose
	RPV	←→ atorvastatin AUC	No dose adjustment necessary
Rosuvastatin	**EFV ETR NVP**	←→ rosuvastatin expected	No dose adjustment necessary
Pravastatin	**EFV ETR**	EFV: Pravastatin AUC ↓ 44% ETR: ↓ pravastatin possible	Adjust statin dose according to lipid response, but do not exceed the maximum recommended dose

Concomitant Drug Class	NNRTI	Description of Interaction	Suggested Management
Immunosuppressants			
Cyclosporine Everolimus Sirolimus Tacrolimus	EFV ETR NVP	↓ immunosuppressant possible	Increase in immunosuppressant dose may be necessary Therapeutic drug monitoring of immunosuppressant is recommended
Narcotics			
Buprenorphine	EFV	Buprenorphine AUC ↓ 50% Norbuprenorphine AUC ↓ 71%	No dose adjustment recommended Monitor for withdrawal symptoms
	ETR	Buprenorphine AUC ↓ 25%	No dose adjustment necessary
	NVP	No significant effect	No dose adjustment necessary
Methadone	EFV NVP	Methadone AUC ↓ 52% (EFV), 37-51% (NVP)	Opioid withdrawal common Increase in methadone dose often necessary
	ETR	No significant effect	No dose adjustment necessary
	RPV	R-methadone AUC ↓ 16%	No dose adjustment necessary Monitor for withdrawal symptoms
PDE5 Inhibitors			
Sildenafil Tadalafil	EFV ETR NVP	↓ sildenafil/tadalafil possible	May need to titrate dose based on clinical effect.
	RPV	←→ sildenafil/tadalafil	No dose adjustment necessary
Others			
St John's Wort	EFV ETR NVP	↓ EFV, ETR, and NVP expected	Avoid co-administration
	RPV	↓ RPV expected	Avoid co-administration

Table 10.3 • Common PIs Drug Interactions

Concomitant Drug Class	PI	Description of Interaction	Suggested Management
Acid reducer			
Antacids	**ATV/r**	↓ ATV (↑ pH ↓ ATV solubility)	Give ATV at least 2 hours before or after antacids or buffered medications
H2 Receptor Antagonists	**ATV/r**	↓ ATV (↑ pH ↓ ATV solubility)	H2RA dose should not exceed a dose equivalent to famotidine 40mg q12h in PI-naive patients or 20mg q12h in PI-experienced patients Administer ATV/r with food simultaneously with and/or ≥10 hours after the dose of H2RA *Note:* *PO Famotidine 20mg q12h = PO Ranitidine 150mg q12h;* *IV Famotidine 20mg q12h = IV Ranitidine 50mg q8h*
Proton Pump Inhibitors (PPIs)	**ATV/r**	ATV/r AUC ↓ 42-76%. (↑ pH ↓ ATV solubility)	Avoid co-administration If co-administration is unavoidable, PPIs should not exceed dose equivalent of omeprazole 20mg OD and should be administered 12 hours before ATV/r
Antibiotics			
Clarithromycin	**DRV/ rLPV/r**	DRV/r : ↑ clarithromycin AUC 57% LPV/r: ↑ clarithromycin expected	Consider alternative macrolide (e.g., azithromycin) If co-administration is unavailable, 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
	ATV/r	↑ clarithromycin expected ↑ ATV/r expected	Consider alternative macrolide (e.g., azithromycin) If co-administration is unavailable, monitor for QTc prolongation
Erythromycin	**All PIs**	↑ erythromycin expected ↑ PIs expected	Consider alternative macrolide (e.g., azithromycin) Anticoagulants and Antiplatelets
Anticoagulants and Antiplatelets			
Apixaban	**All PIs**	↑ apixaban expected	Avoid co-administration
Dabigatran	**ATV/ rLPV/r**	↑ dabigatran expected	Avoid co-administration
	DRV/r	↑ dabigatran expected	No dosage adjustment necessary
Rivaroxaban	**All PIs**	↑ rivaroxaban expected	Avoid co-administration

Concomitant Drug Class	PI	Description of Interaction	Suggested Management
Anticoagulants and Antiplatelets			
Clopidogrel	**All PIs**	Clopidogrel active metabolite AUC ↓69%	Avoid co-administration
Ticagrelor	**All PIs**	↑ ticagrelor expected	Avoid co-administration
Warfarin	**All PIs**	↓ warfarin possible	Monitor INR closely when stopping or starting PI/r and adjust warfarin dose accordingly
Anticonvulsants			
Carbamazepine	**ATV/r LPV/r**	↑ CBZ possible ↓ PI possible	Consider alternative anticonvulsant If co-administration is unavailable, CBZ dose reduction maybe necessary; monitor concentration and virological response
	DRV/r	CBZ AUC ↑ 45% ←→ DRV	Monitor anticonvulsant level and adjust dose accordingly
Lamotrigine	**LPV/r ATV/r**	LTG AUC ↓ 30-50% ←→ PI	Titrate lamotrigine dose to the desired effect or consider alternative anticonvulsant
Phenytoin Phenobarbital	**ATV/r DRVr LPV/r**	↓ Phenytoin possible ↓ Phenobarbital possible ↓ PI possible	Consider alternative anticonvulsant
Valproic Acid	**All PIs**	↓ or ←→ VPA possible LPV AUC ↑ 38% Other PIs: No data	Monitor anticonvulsant level and adjust dose accordingly Monitor PI tolerability
Antidepressants, Anxiolytics and Antipsychotics			
Aripiprazole	**All PIs**	↑ aripiprazole expected	Administer 25% of the usual aripiprazole dose Titrate dose based on clinical monitoring for efficacy/toxicity
Quetiapine	**All PIs**	↑ quetiapine expected	*Starting quetiapine in a patient receiving a PI:* Initiate 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.

Concomitant Drug Class	PI	Description of Interaction	Suggested Management
Antidepressants, Anxiolytics and Antipsychotics			
SSRIs (e.g., escitalopram, fluoxetine, paroxetine, sertraline)	**All PIs**	With DRV/r: Paroxetine AUC ↓39% Sertraline AUC ↓49% ↑ fluvoxamine possible Other PIs: No data	Titrate SSRI dose using the lowest available initial/maintenance dose and based on clinical response
TCA (e.g., amitriptyline, imipramine, nortriptyline	**All PIs**	↑ TCA expected	Titrate TCA using the lowest possible dose and based on clinical assessment Monitor for TCA-related adverse events
Other CYP3A4 and/or CYP2D6 substrates (e.g., perphenazine, risperidone, clozapine)	**All PIs**	↑ antipsychotic possible	Titrate the dose using the lowest available initial/maintenance dose and based on clinical response Monitor for adverse events
Antifungal			
Fluconazole	**All PIs**	No significant effect	No dose adjustment necessary
Isavuconazole	**LPV/r**	Isavuconazole AUC ↑ 96% LPV AUC ↓27% RTV AUV ↓31%	If co-administered, monitor isavuconazole concentration and adverse events Monitor virologic response
	Other PIs	↑ isavuconazole expected ↑ PI possible	If co-administered, monitor isavuconazole concentration and adverse events Monitor PI tolerability
Itraconazole	**All PIs**	↑ traconazole expected ↑ PI possible	Do not exceed itraconazole 200mg/day Use with caution and monitor for toxicities
Posaconazole	**ATV/r**	ATV AUC ↑ 146% ↑ posaconazole possible	If co-administered, monitor posaconazole concentration and adverse events Monitor for PI-related adverse events
	Other PIs	↑ PI possible ↑ posaconazole possible	
Voriconazole	**All PIs**	Low dose RTV 100mg BD ↓voriconazole AUC by 39%.	Co-administration of voriconazole and ritonavir-boosted PIs should be avoided, unless benefits outweighs risks

Concomitant Drug Class	PI	Description of Interaction	Suggested Management
Antimalarials			
Artemether/ Lumefantrine	**ATV/r**	↑ lumefantrine expected	Clinical significance unknown If co-administered, monitor closely for antimalarial efficacy and lumefantrine-related adverse events
	DRV/r	Artemether AUC ↓ 16%, DHA AUC ↓ 18%, Lumefantrine AUC ↓ 2.5-fold ←→DRV	
	LPV/r	Artemether AUC ↓ 40%, DHA AUC ↓ 17%, Lumefantrine AUC ↓ 4.8-fold ←→LPV	
Atovaquone/ Proguanil	**ATV/r**	↓ atovaquone AUC 46% ↓ proguanil AUC 41%	Clinical significance unknown Consider alternative drug for malaria prophylaxis
	LPV/r	↓ atovaquone AUC 74% ↓ proguanil AUC 38%	
Mefloquine	**All PIs**	With RTV 200 mg q12h: RTV AUC ↓ 31%, Cmin ↓ 43%; ←→Mefloquine	Clinical significance unknown Consider alternative drug If co-administered, monitor closely for mefloquine-related adverse events and virologic response
Antimycobacterials			
Rifampicin	**All PIs**	↓ PI by >75%	Contraindicated Avoid co-administration
Rifabutin	**All PIs**	↑ rifabutin AUC at least ~100-200%	If co-administered, the recommended dose is Rifabutin 150mg q24h. Monitor for rifabutin-related adverse events
Benzodiazepines			
Alprazolam Clonazepam Diazepam	**All PIs**	↑ benzodiazepine possible ↑ alprazolam half-life 222% and AUC 248%	Consider alternative benzodiazepines such as lorazepam, oxazepam, or temazepam
Midazolam	**All PIs**	↑ midazolam expected	Avoid co-administration Oral midazolam contraindicated Parenteral midazolam can be used with caution when given as a single dose in a monitored situation for procedural sedation
Zolpidem	**All PIs**	↑ zolpidem possible	Initiate zolpidem at lower dosage and monitor for zolpidem-related adverse events

Concomitant Drug Class	PI	Description of Interaction	Suggested Management
Cardiac Medications			
Antiarrhythmics (e.g., disopyramide, flecainide, lidocaine, propafenone)	**All PIs**	↑ antiarrhythmic possible	Avoid co-administration If co-administered, monitor for antiarrhythmics-related adverse events
Amiodarone	**All PIs**	↑ amiodarone possible ↑ 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 CYP2D6 enzymes (e.g., atenolol, labetalol, nadolol, sotalol)
CCBs (except diltiazem)	**All PIs**	↑ dihydropyridine possible ↑ verapamil possible	Use with caution Titrate CCB dose and monitor closely
Digoxin	**All PIs**	With RTV 200mg q12h: Digoxin AUC ↑ 29%, $t_{1/2}$ ↑ 43% With DRV/r: Digoxin AUC ↑ 36%	Use with caution Monitor digoxin levels Digoxin dose may need to be decreased Titrate initial digoxin dose
Diltiazem	**ATV/r**	Unboosted ATV: Diltiazem AUC ↑ 125% Greater ↑ likely with ATV/r	Decrease diltiazem dose by 50% Initiate with the lowest dose and titrate according clinical response and adverse events ECG monitoring is recommended
	DRV/ rLPV/r	↑ diltiazem possible	Use with caution Adjust diltiazem dose according to clinical response and adverse events
Eplerenone	**All PIs**	↑ eplerenone expected	Contraindicated
Ivabradine	**All PIs**	↑ ivabradine expected	Contraindicated
Ranolazine	**All PIs**	↑ ranolazine expecte	Contraindicated
Corticosteroids			
Budesonide Ciclesonide Fluticasone Mometasone (Inhaled or intranasal)	**All PIs**	↑ glucocorticoid level With RTV 100mg q12h: Fluticasone AUC ↑ 350-fold.	Co-administration can result in adrenal insufficiency and Cushing's syndrome Do not co-administer unless potential benefits outweigh the risks May consider alternative (e.g., beclomethasone)

Concomitant Drug Class	PI	Description of Interaction	Suggested Management
Corticosteroids			
Dexamethasone (Systemic)	**All PIs**	↑ glucocorticoid level ↓ PI levels possible	Consider alternative corticosteroid for long-term use If co-administration is unavoidable, monitor virologic response
Prednisolone (Systemic)	**All PIs**	↑ prednisolone possible With LPV/r: Prednisolone AUC ↑ 31%	Co-administration may be considered if potential benefits outweighs the risks. If co-administered, monitor for adrenal insufficiency and Cushing's syndrome.
Glucose-Lowering Medications			
Saxagliptin **Dapaglifozin/ Saxagliptin**	**All PIs**	↑ saxagliptin expected	Limit saxagliptin dose to 2.5mg
Hepatitis C Direct-Acting Antiviral Agents			
Daclatasvir	**ATV/r**	↑ Daclatasvir	Decrease daclatasvir dose to 30mg/day
	DRV/ rLPV/r	←→ Daclatasvir	No dose adjustment necessary
HMG-CoA Reductase Inhibitors			
Atorvastatin	**All PIs**	Atorvastatin ↑ AUC 3.9 to 9.2-fold	Administer the lowest effective atorvastatin dose (max: 20mg/day) and monitor for adverse events
Lovastatin	**All PIs**	Significant ↑ lovastatin	Contraindicated
Pravastatin	**ATV/r**	No data	Administer the lowest effective pravastatin dose and monitor for adverse events
	DRV/r	Pravastatin AUC ↑ 81% (single dose), ↑ 23% (steady state)	
	LPV/r	Pravastatin AUC ↑ 33%	No dose adjustment necessary
Rosuvastatin	**ATV/r**	Rosuvastatin AUC ↑ 3-fold	Administer the lowest effective rosuvastatin dose (max: 10mg/day) and monitor for adverse events
	LPV/r	Rosuvastatin AUC ↑ 2-fold	
	DRV/r	Rosuvastatin AUC ↑ 48%	Administer the lowest effective rosuvastatin dose and monitor for adverse events
Simvastatin	**All PIs**	Significant ↑ simvastatin	Contraindicated

Concomitant Drug Class	PI	Description of Interaction	Suggested Management
Hormonal Therapies			
Contraceptives: Ethinyl estradiol Norethidrone	**ATV/r**	Ethinyl estradiol AUC ↓ 19% Norethindrone AUC ↑ 51%	Use alternative or additional contraceptive methods Oral contraceptive should contain at least 35mcg of ethinyl estradiol.
	DRV/r	Ethinyl estradiol AUC ↓ 44% Norethindrone AUC ↓ 14%	
	LPV/r	Ethinyl estradiol AUC ↓ 42% Norethindrone AUC ↓ 16%	
Contraceptives: Levonorgestrel Etonogestrel	**All PIs**	↑ levonorgestrel expected ↑ etonogestrel expected	No dose adjustment necessary
Immunosuppressants			
Cyclosporine Sirolimus Tacrolimus	**All PIs**	↑ immunosuppressant expected	Initiate with an adjusted dose of immunosuppressant to account for potential increased concentrations of the immunosuppressant and monitor for toxicities Therapeutic drug monitoring of immunosuppressant is recommended Consult specialist as necessary
Everolimus	**DRV/r**	↑ immunosuppressant expected	Avoid co-administration
	Other PIs	↑ immunosuppressant expected	Initiate with an adjusted dose of immunosuppressant to account for potential increased concentrations of the immunosuppressant and monitor for toxicities Therapeutic drug monitoring of immunosuppressant is recommended Consult specialist as necessary
Narcotics			
Buprenorphine	**ATV/r**	Buprenorphine AUC ↑ 66%	Buprenorphine dose reduction may be necessary Monitor for sedation and signs/ symptoms of overmedication
	DRV/r	←→buprenorphine	No dose adjustment necessary Monitor for buprenorphine-related adverse event
	LPV/r	←→ LPV/r	
Methadone	**All PIs**	Methadone AUC ↓ 16-27% (ATV/r, DRV/r), 26-53% (LPV/r)	Opioid withdrawal is unlikely but may occur Monitor for opioid withdrawal and titrate methadone dose accordingly

Concomitant Drug Class	PI	Description of Interaction	Suggested Management
PDE5 Inhibitors			
Sildenafil	**All PIs**	Sildenafil AUC↑	*For erectile dysfunction:* Initiate with sildenafil 25mg q48h and monitor sildenafil-related adverse events *For PAH:* Contraindicated
Tadalafil	**All PIs**	Tadalfil AUC↑	For erectile dysfunction: Initiate with tadalafil 5mg (do not exceed 10mg q72h) and monitor sildenafil-related adverse events *For PAH in patients on a PI >7days:* Initiate with tadalafil 20mg q24h *For patient on tadalafil for PAH and requires a PI:* Stop tadalafil ≥24hr prior to PI initiation. Restart at 20mg q24h after 7 days on PI
Others			
Colchicine	**All PIs**	Colchicine AUC ↑296%	*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 day. *For prophylaxis of gout flares:* Colchicine 0.3 mg q24-48h Contraindicated in hepatic or renal impairment (CrCl<60 mL/min)
St John's Wort	**All PIs**	↓ PI expected	Contraindicated
Salmeterol	**All PIs**	↑ salmeterol possible	Avoid co-administration because of potential increased risk of salmeterol-related cardiovascular events

Table 10.4 • Common INSTIs Drug Interactions

Concomitant Drug Class	INSTI	Description of Interaction	Suggested Management
Acid reducer			
Aluminium, Magnesium ± Calcium-Containing Antacids	**RAL**	With Al-Mg Hydroxide antacid: RAL Cmin ↓ 49-63% With CaCO3 antacid: RAL Cmin ↓ 32%	Avoid co-administration Use alternative agent No dose adjustment or dosing separation necessary
	DTG	When administered simultaneously with antacid: DTG AUC ↓ 74% When administered 2 hours before antacid: DTG AUC ↓ 26%	Administer DTG at least 2 hours before or at least 6 hours after antacids that contain polyvalent cations.
H2RA	**All INSTIs**	RAL AUC ↑ 44% ↔ DTG	No dose adjustment necessary
PPIs	**All INSTIs**	RAL AUC ↑ 37% ↔ DTG	No dose adjustment necessary
Anticonvulsants			
Carbamazepine Phenobarbital Phenytoin	**RAL**	↔ / ↓ RAL possible	Avoid co-administration
	DTG	With CBZ: DTG AUC ↓ 49%	Increase DTG dose to 50mg q12h in ART-naïve or ART-experienced but INSTI-naïve patients Do not co-administer in INSTI-experienced patients with known or suspected INSTI resistance
		With phenytoin and phenobarbital:↓ DTG possible	Avoid co-administration
Valproic acid	**All INSTIs**	No data	Monitor valproic acid concentration and virologic response
Antidepressants, Anxiolytics and Antipsychotics			
SSRIs **TCAs**	**RAL** **DTG**	↔ SSRI expected ↔ TCA expected	No dose adjustment necessary
Aripiprazo	**RAL** **DTG**	↔ aripiprazole expected	No dose adjustment necessary
Antifungals			
Azoles	**RAL** **DTG**	↔ itraconazole, posaconazole, voriconazole expected ↑ isavuconazole expected ↔ RAL, DTG expected	No dose adjustment necessary

Concomitant Drug Class	INSTI	Description of Interaction	Suggested Management
Antimycobacterials			
Rifampicin	RAL	With RAL 400mg: RAL AUC ↓ 60% With RAL 800mg q12h: RAL AUC ↑ 27%	Consider alternative (e.g., rifabutin) If co-administered, increase RAL dose to 800mg q12h Do not co-administer with RAL 1200mg q24h Monitor closely for virologic response
	DTG	Rifampin + DTG 50mg q12h vs DTG 50mg q12h alone: DTG AUC ↓ 54% Rifampin + DTG 50mg q12h vs DTG 50mg q24h alone: DTG AUC ↑ 33%	Consider alternative (e.g., rifabutin) If co-administered, increase DTG dose to 50mg q12h in patients without suspected or documented INSTI resistance/mutations. In patients with suspected or documented INSTI resistance, consider an alternative agent (e.g., rifabutin). Monitor closely for virologic response
Rifabutin	RAL	RAL AUC ↑ 19%, Cmin ↓ 20%	No dose adjustment necessary
	DTG	DTG AUC ←→, Cmin ↓ 30%	No dose adjustment necessary
Glucose-Lowering Medications			
Metformin	RAL	←→ metformin expected	No dose adjustment necessary
	DTG	Metformin AUC ↑ 79%	Initiate at lowest dose and titrate based on glycaemic control Monitor for metformin-related adverse events Limit total daily dose of metformin to 1000mg
HMG-CoA Reductase Inhibitors			
Atorvastatin Lovastatin Pravastatin Simvastatin	RAL	←→ statins expected	No dose adjustment necessary
Hormonal Therapies			
Contraceptives: Ethinyl estradiol Norgestimate Etonogestrel	RAL DTG	←→ ethinyl estradiol ←→ norgestimate Etonogestrel subdermal implant ↑ 27% ←→ RAL, DTG	No dose adjustment necessary
Menopausal Replacement Therapy	RAL DTG	←→ estrogen expected ←→ drospirenone, medroxyprogesterone, or micronized progesterone expected	No dose adjustment necessary

Concomitant Drug Class	INSTI	Description of Interaction	Suggested Management
Others			
Polyvalent Cation Supplements (Mg, Al, Fe, Ca, Zn, including multivitamins with mineral	**RAL**	↓ RAL possible	If coadministration is necessary, give RAL at least 2 hours before or at least 6 hours after supplements containing polyvalent cations, including but not limited to the following products: cation-containing laxatives; Fe, Ca, or Mg supplements; and sucralfate. Monitor for virologic efficacy. *Many oral multivitamins also contain varying amounts of polyvalent cations; the extent and significance of chelation is unknown.*
	DTG	With $CaCO_3$ under fasting conditions: DTG AUC ↓ 39% With Fe under fasting conditions: DTG AUC ↓ 54% With $CaCO_3$ or Fe with food: ←→ DTG	Administer DTG and supplements that contain Ca or Fe together with food, or administer DTG at least 2hours before or at least 6 hours after supplements Do not co-administer DTG under fasting conditions simultaneously with, or 2 hours after, supplements containing Ca or Fe.
St. John's Wort	**DTG**	↓ DTG possible	Avoid coadministration

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

CHAPTER 11

HIV AND TB CO-INFECTION

INTRODUCTION

Tuberculosis and HIV co-infection can result in an accelerated development of both diseases due to bidirectional interaction between TB and HIV. HIV infection accelerates the development of TB from infection to advanced disease. In turn, TB depletes the CD4 T-lymphocytes count and intensifies the immune-depressed effect of HIV[1]. In 2018, there were an estimated 862 000 new cases of TB worldwide amongst people who were HIV-positive and there were about 251 000 HIV-associated TB deaths. People living with HIV are 20 times more likely to develop active TB disease than people without HIV[2]. A systematic review of 12 randomized controlled trials of 8578 people living with HIV found that preventive treatment reduced the overall risk for TB by 33%[2].

11.1 Latent TB

- All PLHIV who do not have symptoms of active TB should receive treatment for latent TB irrespective of the degree of immunosuppression and ART status[2,13].
- Screening questions for active TB. Presence of any of the following should prompt clinician to investigate for active TB[2,3,13]:
  1. Current cough (any duration), fever, night sweats, or weight loss.
  2. Abnormal chest radiograph (or new chest radiograph findings compared to previous chest radiograph) should prompt clinician to perform further investigations.
- Tuberculin skin test (TST) or interferon gamma release assays (IGRA) testing is not required prior to starting latent TB treatment.

Choice of Latent TB Treatment [2,4]

Regimes	Duration
3HR – Daily rifampicin* (10 mg/kg/day), maximum 600 mg per day + Daily isoniazid (5 mg/kg/day), maximum 300 mg per day + Daily pyridoxine 20 mg	3 months
3HP – Weekly rifapentine + isoniazid[5] Rifapentine: – 10–14.0 kg 300 mg – 14.1–25.0 kg 450 mg – 25.1–32.0 kg 600 mg – 32.1–49.9 kg 750 mg – ≥50.0 kg 900 mg maximum Isoniazid: 15 mg/kg; 900 mg maximum	3 months
4R – Daily rifampicin* (10 mg/kg/day), maximum 600 mg per day	4 months
6H – Daily isoniazid (5 mg/kg/day), maximum 300 mg per day + Daily pyridoxine 20 mg	6 months

* Rifampicin has many potential drug-drug interactions with ART. Cautions should be exercised while using rifampicin.

- There are no significant efficacy differences among those treated with 6 months from those treated with 12 months isoniazid preventive therapy[6].
- There is no evidence or recommendation on when to repeat preventive TB treatment[7].

11.2 Active TB [7,8,13]

- Choice of anti-TB
  - 4 drugs regimen – Isoniazid (H), Rifampicin (R), Ethambutol (E), Pyrazinamide (Z) or fixed-drug combination regime based on weigh
- Duration of anti-TB
  - For patient who is clinically responding, and TB culture showed susceptibility to first line therapy:
    i. Pulmonary: 2 months intensive (HREZ) + 4 months maintenance (HR)
    ii. Extrapulmonary (except bone, joint or meningitis): 2 months intensive (HREZ) + 4 months maintenance (HR)
    iii. Bone or joint: 2 months intensive (HREZ) + 4-7 months maintenance (HR)
    iv. Meningitis: 2 months intensive (HREZ) + 10 months maintenance (HR)

- When to start ART?
  - ART should be started as soon as possible regardless of CD4 count, within first 8 weeks of anti-TB therapy[8].
  - If CD4 is less than 50 cells/uL, to start ART within 2 weeks of anti-TB, if patient is tolerating anti-TB.
  - In TB meningitis, should delay ART after 8 weeks of anti-TB. Initiation of ART within 2 weeks of anti-TB was associated with increased rates of adverse events and increased mortality[9].

11.3 TB-Immune Reconstitution Inflammatory Syndrome (TB-IRIS)

- IRIS may present in two different ways:
  i. 'Paradoxical' worsening of symptoms of a known disease, either at a new body site or at the original body site; or
  ii. 'Unmasking' of an occult opportunistic infection, in which disease that was not clinically apparent prior to ART manifests during ART[10].
- In paradoxical TB-IRIS, clinical features that may occur following commencement of anti-TB include fever, weight loss, worsening respiratory symptoms, lymph nodes enlargement. There may also be transient worsening of radiographic abnormalities[11].
- TB-IRIS is associated with low CD4 count, early initiation of ART and extra-pulmonary TB[12].
- Corticosteroids should be considered for treatment of symptomatic IRIS, with dosages and duration tailored according to response[13]. Anti-TB and ART should be continued. Expert consultation is essential.

11.4 Drug Resistant TB

- If drug susceptible test showed resistant TB of any of the drugs in the standard initial TB regimen, expert consultation is essential[10].

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CHAPTER 12

HEPATITIS B AND HIV CO-INFECTION

Approximately 37 million people worldwide are infected with HIV, and chronic HBV infection affects an estimated 5–20% of people living with HIV[1,2]. The prevalence of HBV among HIV-positive individuals in a tertiary care hospital in Malaysia is 13% (2014)[3]. HIV infection has a significant impact on the natural history of chronic hepatitis B infection. The progression of chronic HBV to cirrhosis, end-stage liver disease, or hepatocellular carcinoma is more rapid in HBV/HIV co-infected persons compared to persons with HBV alone[4].

12.1 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 episodes of reactivation
4. Lower seroconversion rates from HBeAg to anti-HBe antibody
5. Less necroinflammatory activity on liver biopsies but more rapid progression to liver fibrosis and cirrhosis[5]
6. Higher liver-related mortality[6]
7. Decreased treatment response compared with persons without HIV coinfection

12.2 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[7].

Goals of Therapy

The goal of therapy for chronic HBV infection is to improve quality of life and survival of infected patients by preventing progression of the diseases to cirrhosis, end stage liver disease and reducing the risk of hepatocellular carcinoma and liver-related mortality.

1. **In HBeAg Positive Patient:**
   a. Seroconversion from HBeAg to anti-HBe antibody
   b. Achieve a sustained suppression of HBV DNA
2. **In HBeAg Negative Patient:**
   a. Achieve a sustained suppression of HBV DNA

Pre-Treatment Assessments:

a. Detailed history and physical examination – assess for treatment history, alcohol history, hepatotoxic medications and evidence of advanced liver disease
b. Full blood count, renal profile, liver function test, coagulation test
c. Serum HBeAg, antiHBe antibody ± HBV-DNA viral load by PCR (Quantitative)
d. Screening for Hepatitis C co-infection (anti-HCV) as they may share same route of transmission
e. Consider Hepatitis A vaccination if patients is not immune (HAV IgG negative)
f. Stage of liver fibrosis via non-invasive methods (serum biomarkers such as AST to platelet ratio index (APRI), Fibrosis-4 (FIB-4) scoring; or ultrasound-based technology such as liver elastography (Fibroscan). Consider liver biopsy if necessary.

g. Alfa-fetoprotein and ultrasound of liver – hepatocellular carcinoma screening
   - Consider repeating every 6 months in patients with liver cirrhosis, family history of hepatocellular carcinoma, males above 40 years old and females above 50 years old[8].

h. Surveillance of oesophageal varices via upper endoscopy should be offered for patients with cirrhosis[8].
   - Patients with a liver stiffness <20 kPA (measured via liver elastography) and with a platelet count > 150,000 per microliter of blood have a very low risk of having varices requiring treatment, and can avoid screening endoscopy. These patients can be followed up by yearly repetition of transient elastography and platelet count[9].
   - In patients with no varices at screening endoscopy, surveillance endoscopy should be repeated at 2-years intervals[9].
   - In patients with small varices at screening endoscopy, surveillance endoscopy should be repeated at one-year interval[9]. Non-selective beta blockers such as propranolol or carvedilol should be prescribed for primary prophylaxis of variceal haemorrhage.
   - Those patients with variceal bleeding should be co-managed with gastroenterologists / hepatologists.

12.3 Treatment Recommendation for HBV Co-Infection[10]

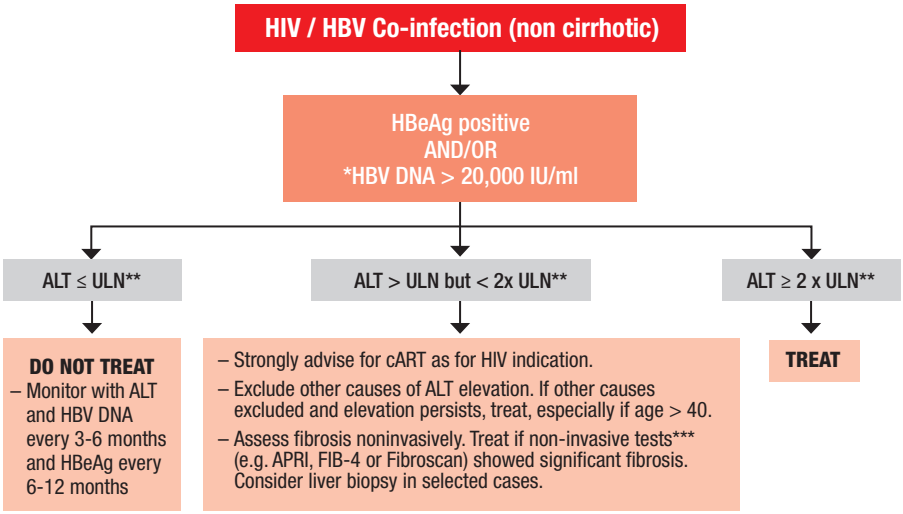
- All patients with chronic HBV should be evaluated to assess the severity of HBV infection. The presence or absence of clinical evidence for cirrhosis might be the key issue in defining treatment strategy in HIV/HBV co-infected patients. Decompensated cirrhosis (Child-Pugh Class B or C) should receive immediate hepatitis B treatment irrespective of ALT or HBV DNA level.
- Patients with chronic HBV should be advised to receive Hepatitis A vaccination (if anti-HAV IgG/Total is negative), abstain from alcohol, and counselled on transmission prevention.
- Important to monitor HBV DNA levels in HIV/HBV co-infected person because elevation of HBV DNA predates ALT abnormalities and in patients with liver cirrhosis the ALT may be normal.
- All HIV/HBV co-infected individuals should be started on cART regardless of CD4 counts with a regime that includes two active drugs against HBV.
- The ARVs regime should consist of a combination of tenofovir disoproxil fumarate (TDF) or tenofovir alafenamide (TAF) and lamivudine or emtricitabine as the NRTI backbone.
- For HIV/HBV co-infected persons with CKD, tenofovir-inclusive regimens may require dose adjustment. TDF-emtricitabine-inclusive regimens require dose adjustment if creatinine clearance < 50 ml/min, and TAF-emtricitabine-inclusive regimens are not recommended in patients with a creatinine clearance < 30 ml/min[10].
- If TDF or TAF is strictly contraindicated, entecavir should be used in addition to a fully suppressive ARV regimen[10].
- In patients with liver cirrhosis, stopping effective anti-HBV treatment is not recommended. This is to avoid flares and decompensation.
- When antiretroviral therapy regimens are altered (e.g., due to HIV resistance or intolerance), drugs that are effective against HBV should not be discontinued unless it is substituted with another drug that has activity against HBV[11].
- The duration of treatment for HIV/HBV co-infection is lifelong.

- HBV DNA should be repeated every 3-6 months to ensure effective HBV suppression. Virologic response is defined as ≥ 2 log10 IU/ml decrease from baseline HBV DNA after 6 months of therapy and a suppressed HBV DNA by one year. In patients who are HBeAg-positive, HBeAg and anti-HBe antibody should be checked to determine if seroconversion has occurred.

In Setting Where HIV/HBV Co-Infected Individuals are not Keen to Initiate cART

- HBV status will become the determining factor to guide physician to initiate therapy.
- In cirrhotic patients, they should be advised for initiation of anti-HBV treatment when the HBV DNA level is detected, irrespective of ALT level. Patients with decompensated cirrhosis and detectable HBV DNA level require urgent anti-HBV treatment irrespective of HBeAg status or ALT level[8].
- For non-cirrhotic patients, decision to treat HBV infection depends on ALT, HBeAg status, HBV DNA levels and whether patient has any evidence of significant liver fibrosis. (Refer Figure 1 and 2)
- Patients who are HBeAg negative, ALT < 2 ULN and HBV DNA < 2000 IU/ml are unlikely to have active viral replication or active liver disease. Hence, anti-HBV therapy is not recommended. However, ALT and HBV DNA need to be monitored regularly.
- On the other hand, patients whose HBeAg positive, ALT ≥ 2x ULN and HBV DNA > 20,000 IU/ml should be counselled for initiation of anti-HBV treatment.
- Anti-HBV treatment like entecavir is recommended in this setting as it does not have activity against HIV[12].

Figure 12.1 • HBV Treatment if HbeAg +ve[10] (but not keen for cART)

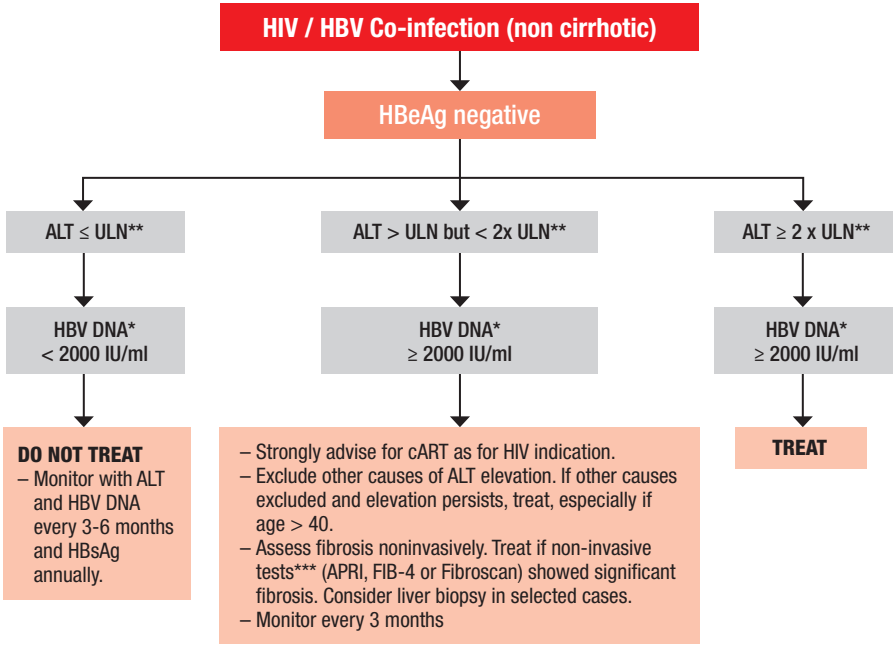


* Patients with HBV DNA 2000-20,000 IU/ml may represent seroconversion. Monitor every 3 months. Treat if persists for > 6 months. Assess fibrosis noninvasively and rule out other causes of elevated ALT. Treat if significant fibrosis and ALT elevation persists.

** The upper limit of normal (ULN) for ALT of 35 U/L for males and 25 U/L for females is recommended to guide management decisions.

*** Significant fibrosis by non-invasive markers means APRI >1.5, FIB-4 > 3.25, and liver stiffness of >9kPa in patients with normal ALT or liver stiffness > 12kPA in patients with ALT> ULN but < 5x ULN (by Fibroscan) [12].

Figure 12.2 • HBV Treatment if HbeAg -ve[10] (but not keen for cART)



* Patients with HBV DNA < 2000 IU/ml and elevated ALT - Rule out other causes of elevated ALT and assess liver fibrosis noninvasively. Treat if significant fibrosis. Monitor every 3 months

** The upper limit of normal (ULN) for ALT of 35 U/L for males and 25 U/L for females is recommended to guide management decisions.

*** Significant fibrosis by non-invasive markers means APRI >1.5, FIB-4 > 3.25, and liver stiffness of >9kPa in patients with normal ALT or liver stiffness > 12kPA in patients with ALT> ULN but < 5x ULN (by Fibroscan)[12].

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CHAPTER 13

MANAGEMENT OF HEPATITIS C AND HIV CO-INFECTION

Treatment for HCV is a priority in HIV/HCV coinfection due to accelerated liver fibrosis progression. It prevents complications associated with liver cirrhosis and viral eradication significantly reduced the rate of extrahepatic deaths.[1]

All HIV-positive persons especially those with HCV risk factors such as ongoing IVDU, chemsex and unprotected anal intercourse, should be screened with anti-HCV antibody test and if positive proceed with HCV RNA or HCV core antigen test to confirm viremic HCV infection. Depending on the risk factor, they should also be linked to harm reduction program such as opioid substitution therapy and counselled regarding the risk of HCV reinfection post treatment.

Initial assessment before initiation of treatment include thorough history, clinical examination and standard blood investigations. It is important not to miss cirrhosis in HCV/HIV coinfection as they should be referred to the hepatologist. With the current pan-genotypic direct acting antivirals (DAA), HCV genotyping is not required even in patients with cirrhosis for certain DAA regime.

For the assessment of liver fibrosis, it is recommended to use non-invasive tests such as the aspartate platelet ratio index (APRI) or Fibrosis-4 (FIB-4) scores to decide on the appropriate treatment duration and regimen, and also to decide if patient requires additional screening for varices (OGDS) or HCC (6 monthly USS and AFP). Meta-analysis show APRI is less accurate in HIV/HCV co-infection compared to HCV mono-infected but the difference was not statistically significant.[2] In a study, FIB-4 was able to accurately predict hepatic fibrosis in HIV/HCV coinfection cohort when compared to liver biopsies thus reducing the need for invasive biopsy.[3] A recent sofosbuvir (SOF) + ravidasvir (RDV) study involving 603 HCV mono infected and HIV-HCV co-infected Malaysian and Thai patients looked at concordance between APRI/Fib-4 score and Fibroscan.[4] The study concluded that APRI score cut off of 1 and FIB4 cut off of 2.2 improved sensitivity while maintaining adequate specificity and negative predictive value to detect liver cirrhosis for the determination of the duration of SOF+ RDV therapy.[4]

$$\text{APRI} = [(\text{AST Level} / \text{AST ULN}) \times 100] / \text{Platelet count } (10^9/\text{L})$$

$$\text{FIB-4} = [\text{AGE} \times \text{AST}] / [\text{Platelet count } (10^9/\text{L}) \times \text{ALT}^{1/2}]$$

For APRI, AST ULN represents the upper limit of normal for AST in the laboratory where these investigations were undertaken.

Table 13.1 • Concordance between Fibroscan and APRI and FIB-4 at Different Cut-Off Values.[4]

Fibrosis staging		Total	APRI						FIB-4v			
			≤2	>2	≤1.5	≥1.5	≤ 1	> 1	≤1.45	>1.45	≤3.25	>3.25
FibroScan®	≤ 12.5 kPa	364 (60%)	355 (59%)	9 (1%)	342 (57%)	22 (4%)	306 (51%)	58 (10%)	239 (40%)	122 (20%)	353 (59%)	8 (1%)
	>12.5 kPa	235 (39%)	149 (25%)	98 (14%)	122 (20%)	113 (19%)	55 (9%)	180 (30%)	36 (6%)	98 (33%)	136 (23%)	98 (16%)
	invalid result	4 (1%)	4 (1%)	0 (0%)	3 (1%)	1 (<1%)	2 (<1%)	2 (<1%)	2 (<1%)	2 (<1%)	3 (<1%)	1 (<1%)

ART initiation is recommended in all HIV-positive persons with HCV co-infection regardless of CD4 count, preferably prior to DAA. Persons with HIV, HCV and HBV triple infection should be initiated on ART regimes which include tenofovir and emtricitabine/lamivudine first.

HCV/HIV co-infection should be offered treatment using pan-genotypic DAA regimens such as sofosbuvir SOF/daclastavir (DCV) or sofosbuvir SOF/ravidasvir RDV, which are highly effective, tolerable with high success rate of sustained virological response (SVR) similar to HCV mono-infection.[5,6] It is important to check for drug-to-drug interactions especially with ART using reliable resources such as the online Liverpool website (https://www.hep-druginteractions.org) and adjust the dose of DAA if necessary. Checking for DDI applies to all concomitant medications prior to starting DAA and at any time a new medication is started while on DAA therapy.

Following the approval of RDV by NPRA, it is now an alternative treatment regimen in Malaysia. It was found to be highly efficacious in PLHIV, difficult to treat genotype 3 infection, with or without compensated cirrhosis, and in those previously treated with interferon-based treatment.6 SOF/RDV regimen was effective (without ribavirin) even in patients with cirrhosis in the STORM-C-1 trial and this enables decentralization and minimizes on-treatment monitoring.[6]

From a study looking at RDV pharmacokinetics and ART drugs interactions, SOF±RDV had no significant impact on emtricitabine and efavirenz concentrations, and tenofovir concentrations were slightly higher but unlikely to be significant.[7] In the STORM-C-1 study, measurement of antiretrovirals plasma concentrations revealed no clinically significant changes in ART concentrations at week 4 compared to before SOF/RDV treatment initiation and no ART dose adjustments were needed.[6]

The choice of DAA to be used for HCV treatment depends on the HIV treatment regime and extent of liver fibrosis. Cirrhotic patients treated with SOF/DAC regime will require the addition of ribavirin. In view of this the preferred regime for cirrhotic patients will be SOF/RDV. All patients with decompensated liver cirrhosis (Child-Turcotte-Pugh class B or C) should be referred to gastroenterologist/hepatologist for treatment. The values mentioned in Table 2 will be used for the evaluation of liver fibrosis.

Table 13.2 • Diagnosis of No Cirrhosis or Compensated Cirrhosis in Chronic Hepatitis C for DAA Therapy.

No cirrhosis	No clinical evidence of cirrhosis and Fibroscan ≤ 12.5 kPA, or APRI ≤ 1.0
Compensated cirrhosis	Clinical evidence of cirrhosis or Fibroscan > 12.5 kPA or APRI > 1.0 and no decompensation (Child-Turcotte-Pugh class A ie 5-6 points)

Note: Clinical evidence of cirrhosis are nodular liver margin and/or splenomegaly on imaging, platelet <150,000 or presence of varices.

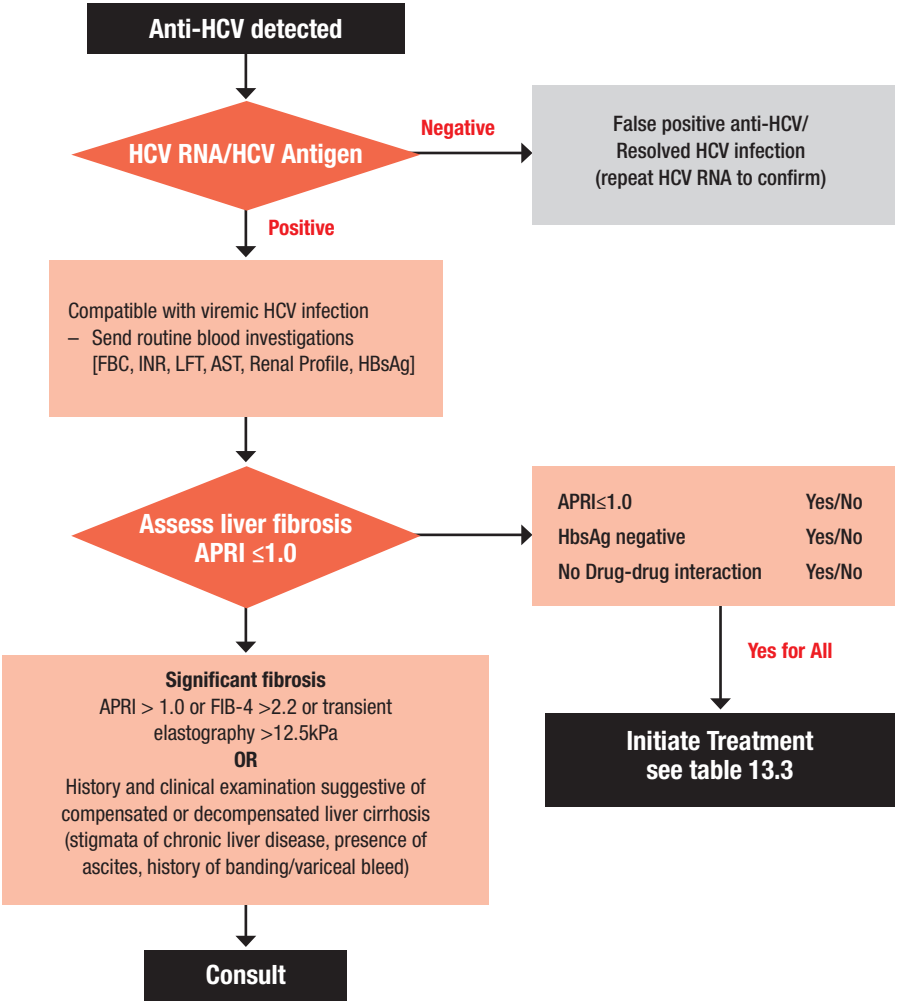
Table 13.3 • Choice of DAA and Duration of Treatment According to HIV Treatment Regime.

HIV treatment regime	Choice of DAA and duration of treatment	
	Without cirrhosis	With compensated cirrhosis
Efavirenz/Nevirapine	SOF 400mg daily & RDV 200mg daily for 12 weeks	SOF 400mg daily & RDV 200mg daily for 24 weeks
Integrase inhibitors – Dolutegravir	SOF 400mg daily & RDV 200mg daily for 12 weeks (based on limited unpublished PK data) OR SOF 400mg daily & DCV 60mg daily for 12 weeks	SOF 400mg daily & RDV 200mg daily for 24 weeks (based on limited unpublished PK data)
Protease inhibitors other than Atazanavir/Ritonavir	SOF 400mg daily & DCV 60mg daily for 12 weeks	Consult
Atazanavir/Ritonavir	SOF 400mg daily & DCV 30mg daily for 12 weeks OR Change HIV regime to alternative protease inhibitors or integrase inhibitors	Consult

For ribavirin-free DAA treatment, the requirement for monitoring is usually minimal. It is advisable to have a scheduled follow up at week 4 to ensure compliance and address adverse events if any. As recommended in the Malaysian 2019 guideline on Management of Chronic Hepatitis C in Adult, the frequency of routine laboratory monitoring (LFT, serum creatinine) shall be limited to weeks 4 and 12 post-DAA treatment. HCV RNA level should be ordered 12 weeks post treatment. If it is undetectable, it is defined as sustained virological response (SVR12) and it is equivalent to cure. After achievement of SVR12, PLHIV should return to standard of care regardless of cirrhosis status. Patients with liver cirrhosis require screening for varices and HCC at diagnosis. After achieving SVR they should continue to have 6 monthly HCC surveillance. For the need of subsequent variceal surveillance, it is recommended to consult the gastroenterologist/hepatologist.

There is evidence that sofosbuvir can be prescribed for CKD stage 4 and 5.[8] It is advisable to liaise with nephrologist and hepatologist for this cohort.

HCV/HIV CO-INFECTION TREATMENT ALGORITHM



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CHAPTER 14

ANTIRETROVIRAL THERAPY AMONG SERODISCORDANT COUPLES

A serodiscordant couple, also known as mixed-status, is when one partner is HIV-negative and the other is HIV-positive.

14.1 Prevention of Transmission from the HIV-Positive Partner

People living with HIV should take ART to treat HIV as soon as possible to improve their own health and prevent transmitting HIV to their sexual partner(s). This is sometimes referred to as treatment as prevention (TasP).

There were 4 multinational studies, HPTN 052, PARTNER, PARTNER2 and Opposites Attract along with several observation studies, with over 4000 couple-years of follow-up, which report a combined HIV transmission risk (while the HIV-positive person was virally suppressed, excluding unconfirmed viral loads) of 0.00 (0.00-0.07) per 100 couple-years[1].

No cases of linked HIV transmission to sexual partners have been documented when the person with HIV was virally suppressed[1].

The overwhelming body of clinical evidence has firmly established the HIV Undetectable = Untransmittable (U=U) concept where "A person living with HIV who has undetectable viral load does not transmit HIV to their partners"

The validity of the U = U concept depends on achieving and maintaining an undetectable viral load in an individual living with HIV[2].

14.2 Couples with Differing HIV Status Who Want to Conceive

For HIV-discordant couples who want to conceive, considerations in choosing the optimal method to achieve pregnancy include transmission risk, treatment efficacy, and affordability.

Safer Conception Strategies Include[3,4]:

1. ART for HIV-positive partners. It is important that they remain adherent to ART and achieve sustained viral suppression (2 recorded HIV viral load result which were below detectable levels at least 3 months apart) before attempting conception.
2. Pre-exposure prophylaxis (PrEP) for HIV-negative partners in situation where their HIV-positive partners have not achieved viral suppression yet or viral suppression status are not known.
3. Assisted reproductive technologies like artificial insemination
4. Both partners should be screened and treated for any sexually transmitted infections before attempting to conceive.

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CHAPTER 15

ANTIRETROVIRAL THERAPY AND ILLICIT DRUG USERS

Substance Use Disorders Among People with HIV

Substance use disorders (SUDs) are prevalent among people with HIV and contribute to poor health outcomes; therefore, screening for SUDs should be a routine part of clinical care.

Substance use may increase the likelihood of risk-taking behaviors (e.g., risky sexual behaviors), the potential for drug-drug interactions, and the risk or severity of substance-associated toxicities (e.g., increased hepatotoxicity or an increased risk of overdose).

Illicit drug users often have difficulties accessing HIV care and are less likely to receive antiretroviral therapy compared to other populations.[1] Evidence indicate that illicit drug users benefit significantly from 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.

Illicit drug users should undergo evaluation and treatment for concurrent mental health disorders.

15.1 HIV Treatment among Illicit Drug Users / IDUs

Methadone and Antiretroviral Therapy

Reduction in substance use and enrollment in an opiate substitution treatment plan, such as methadone maintenance treatment, are associated with improved ART adherence.[2]

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]

Buprenorphine and Antiretroviral Therapy

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

Suboxone (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. Suboxone 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 suboxone is used concomitantly with ARVs.

For details of drug-drug interactions please refer to the Chapter 10 of this guideline.

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POST-EXPOSURE PROPHYLAXIS (PEP) FOLLOWING OCCUPATIONAL EXPOSURE

The most common occupational exposure to HIV among healthcare worker (HCW) is needlestick/ sharp injuries

16.1 Risk for Occupational Transmission of HIV to HCWs

Prospective studies of occupational transmission of HIV to HCWs have estimated that the average risk for transmission after a percutaneous exposure to HIV-infected blood is approximately 0.3% or 1 in 300 (95% CI = 0.2 to 0.5%) and 0.09% or 9 in 10000 (95% CI = 0.0006 to 0.5%) after mucous membranes exposure.[1] The risk of exposure to fluids or tissues has not been quantified but is probably lower than that of HIV-infected blood exposure.

16.2 Factors that may Increase the Risk of HIV Transmission

1. High viral load - risk of transmission from a HIV patient with undetectable serum viral load is thought to be low
2. Deep injury with hollow bore needle[2]
3. Types of body fluids–high risk body fluid that carry significant risk include blood or visibly bloody fluids and other potentially infectious materials (OPIM) (e.g., semen, vaginal secretions, breast milk, cerebrospinal fluid, synovial fluid, pleural fluid, peritoneal fluid, pericardial fluid, and amniotic fluid.) Exposure to non-bloody saliva, tears, sweats, nasal secretions, vomitus, urine or feces does not require PEP[3]
4. Advanced HIV 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.[4] There are also concerns regarding risk of HIV transmission after percutaneous injuries from discarded needles. A case of HIV infections from such injuries have been documented.[5]

16.3 Types of Exposures in which PEP is Indicated

1. 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 fluids or OPIM or that has been from the source patient's blood vessel.
2. Bite from a patient with visible bleeding in mouth that causes bleeding in the exposed worker.
3. Splash of blood, visibly bloody fluids or OPIM to a mucosal surface (mouth, nose, or eyes)
4. Exposure of non-intact skin (e.g., Dermatitis, chapped skin, abrasion or open wound) to blood, visibly bloody fluid or OPIM

16.4 Immediate Management of Individuals with Known or Suspected Exposure to HIV

Wash wound or skin sites that have been in contact with blood or body fluids with soap and water

Irrigate mucous membranes and eyes (remove contact lens) with saline and water

Do not inject antiseptics or disinfectants into wound

Do not squeeze the wound as it may promote hyperaemia and inflammation at the wound site, thus potentially increasing the risk of systemic exposure to HIV if present in the contaminating fluid.

16.4.1 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 exposure, PEP with a 2-drug regimen must be immediately initiated while awaiting final decision.[6]

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 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 disease physician.

16.4.2 HIV Status of the Exposed HCW

Baseline testing of the HCW 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 16.1 • PEP Recommendations When Exposed to HIV Positive Source Patient

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

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

16.5 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 the 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 place where the needle was found and the likelihood of the sharp having been used recently. The needle should not be sent for HIV testing.

There is no documented HIV infection from percutaneous injuries from needles discarded in public settings.[7]

The injuries typically involve small-bore needles that contain only limited amounts of blood, infectiousness of any virus present might be low.[8,9]

Table 16.5.1 • Choice of ARV in PEP

2 drug regime	3 drug regime
Preferred Tenofovir* 300mg OD + Emtricitabine* 200mg OD	**Add** **Preferred** Raltegravir 400mg BD/ Dolutegravir 50mg OD
Alternative Zidovudine 300mg BD + Lamivudine* 150mg BD	**Alternative** Lopinavir / Ritonavir 2 tab BD

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

16.6 Timing of Initiation of PEP

All efforts have to be made to initiate PEP as soon as possible, preferably within 2 hours of exposure. A first dose of PEP should be offered while investigations are underway. PEP should be offered while awaiting information about the source patient or results of the exposed HCW's baseline HIV test. Animal studies have shown that PEP is most likely to be effective when initiated within 24-36 hours.[10,11,12] Time duration beyond which PEP should not be administered is not certain. Decisions regarding PEP beyond 72 hours should be made on a case-by-case basis.

16.7 Duration of PEP

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

16.8 Recommended Follow Up of HCWs

All healthcare 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, evaluation of adherence to PEP 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.

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.

During the 12 week follow up period, HIV-exposed healthcare workers should be advised to use condoms to prevent potential sexual transmission; avoid pregnancy and breast feeding in female HCWs; and refrain from donating blood, plasma, organ, tissue, or semen.

Table 16.2 • Monitoring after Initiation of PEP

Test	Baseline	Week 2	Week 4	Week 12
HIV serology (HIV Ab and HIV Ag whenever possible)	/		/	/
Hepatitis B serology (HBsAg, Anti-HBs, and Anti-HBc)*	/		/	/
Hepatitis C serology (if HepC Ab positive check HCV PCR)	/		/	/
FBC^, RP, LFT	/	/	/	

* Individuals with evidence of previous immunity to hepatitis B (HBsAb positive) will require no further follow-up. Non-immune individuals require immunization and follow-up (to 6 months). See ^ if on zidovudine

Co-infection (HIV + Hep C) in the source patient has been associated with late seroconversions in the recipient HCW, so 24-week and longer follow up testing up to a year should be considered in these cases[13]

16.9 Responsibilities of Hospital Administrators

All hospitals must have a comprehensive plan to manage exposed HCWs. The following details must be included in the plan:

1. The person in-charge of performing counseling and post-exposure evaluation to determine the need for PEP during and after office hours
2. The availability of ARVs needed for PEP within 2 hours of an exposure during and after office hours
3. The availability of 3 to 5 days' supply of PEP to be made available for use especially on weekends and public holidays
4. Funding for ARV drugs

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NON-OCCUPATIONAL POST-EXPOSURE PROPHYLAXIS (nPEP)

17.1 Introduction

Situations that may prompt request for nPEP include:

1. Unprotected vaginal or anal sex
2. Protected sex with condom failure (slippage or breakage)
3. Unsafe needle sharing
4. Non-consensual sex where there is a high probability that the assailant is HIV positive

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

17.2 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.

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

1. Assessment of HIV risk following type of exposure (Refer Table 17.1)
2. HIV and STI testing and treatment
3. Prevention and risk-reduction counselling
4. Clinicians with expertise in the use of ART
5. Timely access to care and initiation of nPEP

Table 17.1 • HIV risk following type of exposure

Type of Exposure	Estimated risk of HIV transmission per exposure from a known HIV-positive individual not on ART
Receptive anal intercourse	1 in 90
Receptive anal intercourse with ejaculation	1 in 65
Receptive anal intercourse no ejaculation	1 in 170
Insertive anal intercourse	1 in 666
Insertive anal intercourse not circumcised	1 in 161
Insertive anal intercourse and circumcised	1 in 909
Receptive vaginal intercourse	1 in 1000
Insertive vaginal intercourse	1 in 1,219
Semen splash to eye	<1 in 10,000
Receptive oral sex (giving fellatio)	<1 in 10,000
Insertive oral sex (receiving fellatio)	<1 in 10,000
Blood transfusion (one unit)	1 in 1
Sharing injecting equipment (includes chemsex)	1 in 149
Human bite	<1 in 10,000

Adapted from BASHH UK guideline for the use of HIV post exposure prophylaxis following sexual exposure (PEPSE) 2021

A Immediate Management and Assessment of an Individual with Known or Suspected Exposure to HIV:

- 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 the wound
- Irrigate mucous membranes or eyes (remove contact lenses) with water or saline

B 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.

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

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 17.2 • Assessing the Need of nPEP Based on Exposure

	Index of HIV Positive		Index of Unknown HIV Status	
	HIV VL unknown or detectable	HIV VL undetectable	From high prevalence country / risk-group (e.g. MSM)*	From low prevalence country / group
SEXUAL EXPOSURES				
Receptive anal sex	Recommend	Not recommended [b]	Recommend	Not recommended
Insertive anal sex	Recommend	Not recommended [b]	Consider[c,d]	Not recommended
Receptive vaginal sex	Recommend	Not recommended [b]	Generally not recommended[c,d]	Not recommended
Insertive vaginal sex	Consider[c]	Not recommended	Generally not recommended[c,d]	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

Adapted from BASHH UK guideline for HIV risk post exposure prophylaxis (PEPSE)

Recommended: the benefits of PEP are likely to outweigh the risk, PEP should be given unless there is a clear reason not to.
Consider: the risk of HIV transmission is low, the risk / benefit balance of PEP is less clear. The risk should be assessed on a case by case basis taking into consideration factors shown in footnotes c and d below.
Generally not recommended: the risk of HIV transmission is very low, the potential toxicity and inconvenience of PEP is likely to outweigh the benefit unless there is a clear specific extenuating factor which increases the risk (see footnotes c, d, e, f below). We anticipate PEP should very rarely be given when the risk has been assessed and discussed
Not recommended: the risk of HIV transmission is negligible and PEP should not be given.

[a] High prevalence countries or risk-groups are those where there is a significant likelihood of the index case individual being HIV positive.
[b] The index case has been on ART for at least 6 months with an undetectable plasma HIV viral load at the time of last measurement and within the last 6 months, with good reported adherence. Where there is any uncertainty about HIV VL results or adherence to ART then PEP should be given. The viral load threshold considered 'undetectable' in the PARTNER 1 and 2 and HPTN052 studies was <200 copies/ml.
[c] Factors that influence decision-making in all exposures: More detailed knowledge of local HIV prevalence within high risk groups, the risk may be greater and where there is doubt PEP should be given
[d] HIV prevalence amongst IDUs varies considerably depending on whether there is a local outbreak and 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

C Factors that Increase the Risk of HIV Transmission Include:

- Receptive anal intercourse
- High plasma viral load (HIV seroconversion or with advanced disease)
- Sexually transmitted infections in the source or exposed individual, especially genital ulcer disease and symptomatic gonococcal infections
- Breach in genital mucosal integrity (eg trauma, genital piercing or genital tract infection)
- Breach in the oral mucosal integrity when performing oral sex
- Intra-arterial injection with a needle or syringe containing HIV-infected blood
- Cervical ectopy
- Menstruation
- Ejaculation

17.3 Behavioural Intervention and Risk-Reduction Counseling

- 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 psychiatry 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).

17.4 Timing and Option for nPEP

- Ideally should be initiated as soon as possible after exposure, but can be considered up to 72 hours
- Duration: 28 days
- Recommended combination for nPEP flow (Table 17.3)

Table 17.3 • Flow Chart for Initiation of nPEP:

STEP 1: If nPEP Recommended or Considered

↓

STEP 2: Is Patient Presenting within 72 hours[a]?

↓

STEP 3: Initiate the First Dose of nPEP Regimen

28-DAY REGIMEN — Recommended nPEP Regimen:[b], Tenofovir 300 mg PO once daily + Emtricitabine 200 mg PO once daily

PLUS

Dolutegravir 50 mg PO once daily OR Raltegravir 400 mg PO twice daily

↓

STEP 4: Baseline Testing

BASELINE TESTING OF EXPOSED PERSON:

- HIV test (4th generation)* HBsAg / HBsAb / HCV Ab
- Pregnancy test for women
- Gonorrhoea/Chlamydia NAAT (based on site of exposure)
- RPR / TPHA 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 turnaround time <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 result is negative but there may have been exposure to HIV in the previous 6 weeks, obtain plasma HIV 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 counseling
- Refer to psychiatry and/or substance use programs when indicated; consider need for intensive risk-reduction counseling services and discuss future use of PrEP with persons with ongoing risk behavior

[a] **Decisions to initiate nPEP beyond 72 hours post-exposure is not recommended**, with the realization of diminished efficacy 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 counseling.

[b] If the source is known to be HIV positive, information about his/her viral load, ART medication history, and history of antiretroviral drug resistance should be obtained, when possible, to assist in selection of a nPEP regimen. Initiation of the first dose of nPEP should not be delayed while awaiting this information and/or results of resistance testing. When this information becomes available, the nPEP regimen may be changed if needed in consultation with an ID Physician.

Table 17.4 • Alternative Regimens

NRTI Backbone (2 drugs)	Third Agent
Tenofovir 300 mg + Lamivudine 300 mg once daily **OR** Combivir 1 tablet twice daily (Zidovudine 300 mg + Lamivudine 150 mg)	Kaletra 2 tablets twice daily (Lopinavir 200 mg + Ritonavir 50 mg) **OR** Atazanavir/Ritonavir (300 mg/100 mg) once daily

Notes:

Baseline HIV Testing for the Exposed Individual

- 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 point-of-care (POC) test. Test for HIV should be done as soon as possible before being given a course of nPEP within 3 days of exposure.
- 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 is viewed
- Decision to continue treatment will be based on current guidelines, and should be made in consultation with an 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 immediately
- High level of sustained adherence to nPEP is necessary to reduce the risk of transmitting HIV and decrease the risk of developing drug resistance

Testing for Other STIs

- Ask for symptoms and test accordingly
- Consider screening with NAATs in asymptomatic patients for Gonorrhoea and Chlamydia (if available), based on site of exposure and serological screening for Syphilis
- Do not forget to counsel patient about the risk of acquiring STIs

Pregnancy Resting 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, HBsAb) will identify nonimmune persons who should be provided Hepatitis B vaccination.
- Advice on Hepatitis B vaccination in those who have not been vaccinated

Testing for Hepatitis C Infection (HCV)

- Test for Hepatitis C antibody (HCV Ab) as well

Table 17.5 • Antiretroviral drugs to avoid as nPEP

Drug(s) to avoid	Rationale
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 hepatotoxicity and risk of severe rash
Abacavir	• Potential for hypersensitivity reactions

17.5 Special situations: Individuals who are on PrEP

Switching from PrEP to nPEP is only recommended if:

- The exposure risk warrants 3-drug nPEP, AND adherence to PrEP is questionable (has been < 4 doses in the week of the exposure), AND the last exposure event occurred within the 72-hour nPEP window
- Risk reduction counselling, non-adherence assessment and intervention need to be emphasized
- Test for HIV at nPEP initiation and completion
- Recommence PrEP on completion of 28 days of nPEP

Transitioning from nPEP back to PrEP

- HIV status should be confirmed as negative at 12 weeks post nPEP. However, individuals at risk may never be out of the serological testing window and PrEP initiation may be a matter of urgency
- Individuals should be tested for HIV at the end of their nPEP course and transitioned immediately onto PrEP.

Table 17.6 • 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 coreantibody	√	√	—	—	√[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 post exposure 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 point-of-care (POC) test
- HIV testing at 4- 6 weeks and 3 months is recommended after significant exposures, regardless of whether the individual accepts or declines nPEP 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 nPEP regime

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PRE-EXPOSURE PROPHYLAXIS (PrEP)

Pre-exposure prophylaxis (PrEP) for HIV involves taking one tablet daily or prior to at-risk events by HIV-negative individuals to prevent HIV infection through sex or sharing needles. It reduces HIV transmission from sex by 99% if taken daily (tenofovir disoproxil/emtricitabine) in men who have sex with men[1] (MSM) and by 75% in heterosexual partners[2]. The efficacy in injecting drug users with high adherence is 74% with tenofovir disoproxil (TDF) alone[3]. The decision for PrEP should be made after careful assessment of current HIV status and the presence of any contraindications, and preferably be incorporated into a preventive service that includes adherence counselling and screening for other sexually transmitted infections (STI).

18.1 Persons Recommended for PrEP[4]

18.1.1 PrEP should be considered in HIV-negative individuals who are:

1. MSM and are sexually active within the last 6 months, with any of the following:
   - a partner who is HIV positive (see 18.1.2).
   - inconsistent use of condoms (for either insertive or receptive anal sex).
   - an STI (syphilis, gonorrhoea or chlamydia) in the last 6 months.
   - individuals requesting PrEP.

2. Heterosexual (men or women) and are sexually active within the last 6 months, with any of the following:
   - a partner who is HIV positive (see 18.1.2).
   - inconsistent use of condoms with partners of **unknown status from high risk groups** (MSM, IDU, Sexual Worker, Transgender)
   - an STI (syphilis, gonorrhoea or chlamydia) in the last 6 months.

3. People who inject drugs (PWID) with any of the following:
   - the use of shared drug injecting equipment.
   - at risk of HIV acquisition from sex.

4. Transgender (men or women) and are sexually active within the last 6 months, with any of the following:
   - a partner who is HIV positive (see 18.1.2).
   - inconsistent use of condoms with partners of unknown status (for either insertive or receptive anal sex).
   - an STI (syphilis, gonorrhoea or chlamydia) in the last 6 months.

5. Consider PrEP in any person engaged in transactional sex and any person practicing chemsex* that is unprotected.

*Chemsex is sexual activity while under the influence of stimulant drugs such as methamphetamine or mephedrone.

18.1.2 Considerations when the partner is HIV positive.

1. If the HIV-positive partner is on effective antiretroviral therapy for ≥6 months **AND** has a viral load of <200 copies/L, studies have shown no risk of transmission, and PrEP is not required[5].

2. However, PrEP can provide additional protection in certain situations.
   - As a bridge when the HIV-infected partner has been taking ART for <6 months.
   - If the partners' treatment status or viral load is unknown.

18.2 Initial Clinical Assessment and Counselling

18.2.1 Assessment may include the following.

1. Screening for symptoms of HIV seroconversion within the past 4 weeks.
2. Reviewing the need for and willingness to take PrEP.
3. Reviewing the client's current medication list for interactions (caution with high dose non-steroidal anti-inflammatory drugs).
4. Whether the client has the means to pay for PrEP.
5. Evaluating fertility goals and contraception use in women who are PrEP candidates.
   - Depot medroxyprogesterone acetate (DMPA) is associated with an increased risk of HIV infection[6]. If at risk of HIV infection, consider alternative contraception whether or not they opt for PrEP.

18.2.2 Counseling and Education should include the following.

1. The limitations of PrEP, and to advise continued use of condoms.
   - PrEP does not provide 100% protection against HIV.
   - PrEP does not protect against STIs and pregnancy.
2. The importance of adherence.
3. It is possible to stop PrEP when moving out of "seasons of risk".
4. The lead-in time to protection and stopping PrEP (see table 18.1).
5. Symptoms of HIV seroconversion, that will require assessment.
6. Potential adverse effects.
   - Start-up syndrome: transient nausea, abdominal cramping, or headache.
     – mild and self-limiting
     – do not require discontinuing PrEP
     – can be managed with simple analgesics and antiemetics
   - Long-term safety (see chapter 8 on ARV adverse effects).
7. Confirming schedule for follow-up and testing.

18.3 Baseline Laboratory Testing (summarized in table 18.3)

18.3.1 HIV Testing[7]

1. 4th generation HIV test. (Preferred whenever available)
   - Combined antigen/antibody laboratory HIV test (EIA) at baseline or a recorded negative test within the previous 4 weeks if no recent exposure.

2. Blood-based point of care test (POCT).
   - 4th generation (antigen/antibody).
   - We recommend that POCT is done at the same time as a combined antigen/antibody laboratory HIV test if available.

- If POCT is negative and the client has no symptoms suggestive of acute HIV, clinicians should start same-day PrEP while awaiting the laboratory test results.

3. HIV nucleic acid amplification test (viral load) can be considered in clients:
   - with symptoms of HIV seroconversion.
     – defer PrEP until HIV nucleic acid amplification test is negative
   - whose initial HIV test is negative but have reported engaging in unprotected sex with an HIV-infected partner or partner of unknown HIV status within the past month.
     – PrEP doesn't need to be deferred BUT repeat a 4th generation EIA after one month.

4. HIV self-testing (HIVST)[8]
   - Is when a person collects their own specimen (oral fluid or fingerprick whole blood) using a simple rapid HIV test and then performs the test and interprets their result.
   - Using WHO prequalified HIVST products[9].
   - It can be used to complement existing HIV testing strategies for oral PrEP services and reduce clinic visits (such as delivery outside of health facilities).
   - May increase PrEP use, persistence, and HIV testing frequency.
   - Can be considered when starting, re-starting and continuing oral PrEP.
   - May be preferred for convenience, privacy and self-managed care.

18.3.2 Other tests[7]

1. Renal function test
   - PrEP should not be initiated if eGFR < 60 mL/min.
   - The requirement for renal function testing depends on age and the presence of kidney related comorbidities[8]. (refer to Table 18.1)
   - Waiting for the renal function test results should not delay the initiation or continuation of PrEP.

Table 18.1 • Suggested Procedures for Measuring Renal Function for TDF-Containing Oral PrEP

Population	Measurement of renal function at:	
	Initiation	Follow-up
< 30-years-old and no kidney-related comorbidities[a]	Optional	• If no initiation test is conducted or if the initiation test is normal,[b] follow-up is optional • If the initiation test result suggests at least mild loss of kidney function,[c] follow-up measurements every 6–12 months are suggested
30–49 years old and no kidney-related comorbidities[a]	Optional/conduct once, at or within 1–3 months of initiation[d]	• If the initiation test is normal,[b] follow-up is optional • If the initiation test result suggests at least mild loss of kidney function,[c] follow-up measurements every 6–12 months are suggested

Population	Measurement of renal function at:	
	Initiation	Follow-up
• ≥ 50 years old and no kidney-related comorbidities[a] • Any age with kidney-related comorbidities[a] • Previous measurements of kidney function suggest at least mild loss of kidney function[c]	Conduct once, at or within 1–3 months of initiation	Follow-up measurements every 6–12 months

eGFR: estimated glomerular filtration rate; PrEP: pre-exposure prophylaxis; TDF: tenofovir disoproxil fumarate.

[a] Kidney-related comorbidities include chronic kidney disease or risk factors such as diabetes or hypertension. There may be an increased risk of kidney-related adverse events during pregnancy, and conditions such as preeclampsia may cause kidney impairment, so more frequent kidney function testing may be considered during pregnancy.

[b] eGFR ≥90 mL/min per 1.73 m^2 or creatinine clearance of ≥90 mL/min.

[c] eGFR <90 mL/min per 1.73 m^2 or creatinine clearance of <90 mL/min.

[d] Risks of kidney impairment and kidney-related adverse events remain low among those aged 30–49 years without kidney-related comorbidities, particularly those aged 30–39, so kidney function monitoring can be considered optional in this group, too, depending on available resources.

Adapted from the Differentiated and simplified pre-exposure prophylaxis for HIV prevention: update to WHO implementation guidance: technical brief 2022.[8]

2. Urinalysis
   - Can be considered if there is a reduction in eGFR.
3. Hepatitis B surface antigen
   - Can be considered if there is a reduction in eGFR.
   - Testing PrEP users for HBV surface antigen (HBsAg) once, at or within one to three months of PrEP initiation, is strongly encouraged where feasible[8].
   - PrEP can be initiated before HBV test results become available.
   - Hepatitis B virus (HBV) infection is not a contraindication for Event Driven-PrEP[8].
   - A referral to a hepatologist is recommended if positive.
4. Pregnancy testing in women.
   - If a woman is pregnant, known risks and benefits should be discussed.
   - If the risk for HIV is ongoing, the client may still benefit from PrEP.
   - Consider appropriate contraception in women of childbearing age.
5. Liver function test can be done for baseline documentation.
6. STI screen
   - Enquire about symptoms of STIs (e.g. sore throat, dysuria, vaginal or penile or rectal discharge, genital lesions)
   - Nucleic acid amplification test (NAAT) for Neisseria gonorrhoea (NG) and Chlamydia trachomatis (CT) is recommended in symptomatic and asymptomatic individuals.
     – Site of screening based on exposure (i.e. genital, rectal and pharyngeal) or pooling of specimens from 3 different sites into one sample (urine) to reduce costs.
     – Standard tests (NG– smear and culture/CT– EIA) based on local practice if NAAT is unavailable.
   - Syphilis (VDRL/RPR +/- TPHA/TPPA).

7. Serology for Hepatitis A, B and C viruses (Hep A-IgG, antibodies-Hep B and antibodies-Hep C virus).
    - HCV antibody testing is strongly encouraged at or within one to three months of PrEP initiation and every 12 months after that, where PrEP services are provided to populations at high risk of HCV infection[8].
    - Vaccination for hepatitis B is recommended in clients with antibody levels below protective levels (< 10 IU/L).
    - Consider offering hepatitis A vaccine to at-risk individuals.

18.4 Prescribing PrEP

18.4.1 When first starting (or when re-starting) PrEP, we recommend that the first prescription is only for a 90-day supply of tenofovir disoproxil fumarate/emtricitabine (TDF-FTC).

- This helps to ensure that the client performs repeat HIV testing and returns for clinical review and treatment monitoring.

18.4.2 Daily dosing PrEP

1. Recommended for anyone at high risk of HIV.
2. Tenofovir disoproxil fumarate/emtricitabine fixed-dose combination, 1 tablet per day.
    - TDF-FTC (300mg/200mg)

18.4.3 Event-driven PrEP (also known as 2+1+1)[8,10.] (Refer to Figure 18.1-18.3)

1. Event-driven PrEP can be discussed and offered to cisgender men and trans and gender diverse people assigned male at birth who are not taking exogenous estradiol-based hormones[8].
2. A loading dose of two tablets of TDF-FTC taken 2–24 hours before sex, followed by a third (one) tablet 24 hours and a fourth (one) tablet 48 hours later, is advised[10].
3. Where potential exposure is sustained over more than 24 hours, one pill per day should be taken until the last sexual intercourse, followed by the two post-exposure pills[10].
4. When re-starting PrEP, clients are advised to take a loading dose of two pills[10].
    - UNLESS the last PrEP dose was less than 7 days earlier, in which case, they only need one pill to load.

18.4.4 Contraindications

1. eGFR < 60 ml/min.
2. HIV positive or evidence of possible acute HIV infection.
3. Known allergies to any of the PrEP components.
4. Unable or unwilling to do follow-up HIV testing and return for safety monitoring visits.

18.5 Starting, Using and Stopping PrEP

Table 18.2 • Starting, using and stopping TDF-based oral PrEP safely

Population	Starting oral PrEP	Using oral PrEP	Stopping oral PrEP
Cisgender men and trans and gender diverse people assigned male at birth[a] who: • have sexual exposure AND • are not taking exogenous estradiol-based hormones	Take a double dose 2–24 hours before potential sexual exposure (ideally closer to 24 hours before potential exposure)	Take one dose per day	Take one dose per day until two days after the day of the last potential sexual exposure
Cisgender women and trans and gender diverse people assigned female at birth[a] Cisgender men and trans and gender diverse people assigned male at birth[a] who are taking exogenous estradiol-based hormones People using oral PrEP to prevent HIV acquisition from injecting practices	Take one dose daily for seven days before potential exposure	Take one dose per day	Take one dose daily for seven days after the last potential exposure

PrEP: pre-exposure prophylaxis; TDF: tenofovir disoproxil fumarate.

[a] "Trans and gender diverse people" is an umbrella term for those whose gender identity, roles and expression does not conform to the norms and expectations traditionally associated with the sex assigned to them at birth; it includes people who are transsexual, transgender, or otherwise gender nonconforming or gender incongruent. Transgender people may self-identify as transgender, female, male, transwoman or transman, trans-sexual or one of many other gender nonconforming identities.

Adapted from the Differentiated and simplified pre-exposure prophylaxis for HIV prevention: update to WHO implementation guidance: technical brief 2022.[8]

18.6 Clinical Follow-Up and Monitoring of PrEP

18.6.1 For the frequency of follow-up and monitoring tests, please see table 18.3.

Table 18.3 • Baseline, Follow-Up, and Monitoring of PrEP

Test	Baseline	1 month	3 months	Every subsequent 3-6 months while on prEP	Comment
HIV test	✓	✓	✓	✓	See HIV testing 18.3.1
Assess for: • symptoms of seroconversion • need for PrEP • adherence	✓	✓	✓	✓	Clients with symptoms suggestive of seroconversion should be investigated with a combined HIV antigen/antibody test and HIV viral load.
Renal profile Calculate eGFR every visit	✓	✓	✓	✓	The frequency of repeat renal function testing depends on age, comorbidities and risk factors for CKD,and absence/ presence of GFR < 90 at any time.[8] See table 18.1. If eGFR <60ml/min, stop PrEP and investigate for reversible causes.
Hepatitis B surface antigen (HBsAg)	✓				Annual screening is recommended if not vaccinated.
Urine pregnancy test (if indicated)	✓	✓	✓	✓	Consider appropriate contraception.
STI screening by symptoms	✓	✓	✓	✓	Consider risk reduction counselling.
Anti-HCV	✓				Hep C Ab testing is strongly recommended at or with in the 1st 3 months of PrEP initiation and every 12 months in populations at high risk of HCV infection
Optional					
STI-NAAT (NG & CT) or as per local practice	✓		✓	✓	3-6 monthly intervals depending on accessibility to test.
Screening for syphilis RPR/VDRL ± TPHA/TPPA	✓		✓	✓	3-6 monthly intervals depending on accessibility to test.
Anti-HBs antibody	✓				Vaccinate if antibody ≤10 IU/L.
Anti-HAV or IgG-HAV	✓				Vaccinate if antibody negative (MSM and others at risk)

18.7 Special Situations

1. Post-exposure prophylaxis following suboptimal adherence to PrEP.
   - If fewer than four tablets have been taken within the last 7 days or where the last dose was more than 7 days ago, PEP should be given.
2. Acute kidney injury while on PrEP.
   - Abnormal CrCl results of < 60 ml/min should be repeated on a separate day before stopping oral PrEP.
   - Discontinue TDF/FTC if renal impairment is persistent (eGFR < 60 ml/min).
   - If a different cause for renal impairment is found and removed, and renal function has improved ≥ 60 ml/min, PrEP can be tried again with close monitoring of renal function.
3. Seroconversion while receiving PrEP:
   - Once HIV infection is confirmed, stop PrEP immediately and refer to a tertiary centre as soon as possible.
   - Resistance testing should be done before starting the client on ART.
4. Chronic hepatitis B.
   - TDF-FTC is used to treat Hepatitis B, and there is a risk of rebound viremia and hepatic flare upon stopping.
     - Educate the patients on symptoms of an acute flare of hepatitis B.
     - Continue to monitor clinically and with liver function tests after stopping PrEP (monthly for 6 months).
     - Consider referring to a hepatologist before stopping PrEP.
5. There are no known interactions between TDF-FTC and feminising and masculinising hormones. Oral PrEP drugs do not raise or lower levels of gender-affirming hormones. Hormones taken by transgender women appear to slightly lower levels of tenofovir but not enough to affect the efficacy of daily PrEP.
6. In clients with recurrent HIV exposure requiring nPEP, it is recommended to transition without a break to PrEP upon completion of PEP.
7. PrEP in pregnancy and breastfeeding needs to be weighed against the risk of transmitting HIV to mother and child and likely will still be.

Figure 18.1 • Event-driven PrEP dosing if sex occurs once a week

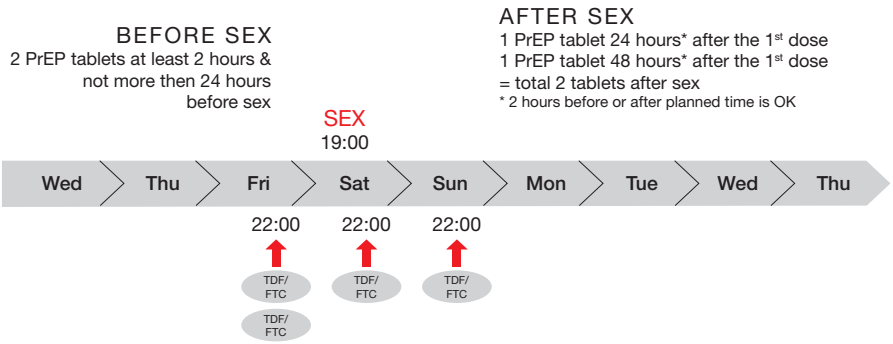


Figure 18.2 • Event-driven PrEP dosing if sex occurs several times during the week

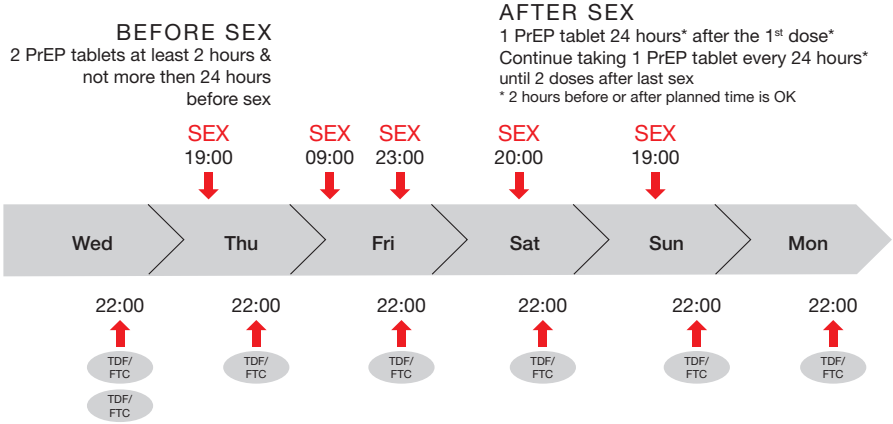
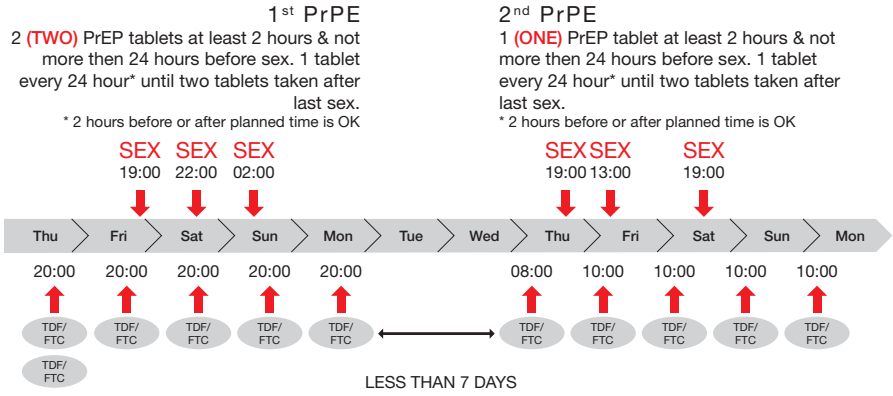


Figure 18.3 • Event-driven PrEP dosing if sex occured several times during a week and then more sex within a week.



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CHAPTER 19

PREVENTION AND MANAGEMENT OF CO-MORBIDITIES IN HIV-POSITIVE PERSONS

19.1 Prevention of Cardiovascular Disease (CVD)

Advancement of antiretroviral therapy over the years has revolutionized the management of patients with HIV disease. It has now changed from a high mortality infection into a chronic illness. People living with HIV is twice more likely to develop cardiovascular disease and global burden of HIV-associated cardiovascular disease has tripled over the past 2 decades[1]. Apart from HIV itself, antiretroviral therapy and traditional risk factors such as hypertension, dyslipidaemia, cigarette smoking and diabetes mellitus play an important role in the pathogenesis of atherosclerotic cardiovascular disease[2]. Studies have shown that suppression of HIV itself is crucial to reduce cardiovascular risk by reducing proinflammatory cytokines and should be the prioritized in all people living with HIV[3].

Assessment and management of cardiovascular risk should be provided for all individuals living with HIV according to standard protocols recommended for the general population. The WHO PEN (Package of Essential Noncommunicable Disease Interventions) targets the following populations for CVD screening[4]:

- Age > 40 years
- Smokers
- People with known hypertension or diabetes mellitus
- Waist circumference > 90cm in women and 110 cm in men
- Family history of diabetes or premature CVD

19.1.1 Assessing Cardiovascular Risk

Assessment of patient's individual risk factors should be part of the initial medical visit.
This includes:

- Fasting lipid level
- Fasting blood glucose and/or Hba1c
- Smoking habit
- Diet and level of exercise activity
- Baseline blood pressure
- Body mass index
- Waist circumference
- Family history of coronary artery disease, diabetes mellitus or hypertension
- Urinalysis to look for proteinuria and glycosuria

Various cardiovascular risk models have been utilized to estimate an individual's risk for the development of coronary heart disease such as Framingham risk score, Pooled Cohort Equations CV Risk Calculator (PCE) and the DAD cohort risk calculator. Although the utility of these calculators in the HIV-infected population may not be optimal, they are likely a reasonable starting point for assessing risk[5]. One of the risk scores that is widely used in Malaysia is the Framingham Risk Score that assesses the 10-year risk of developing CVD (Table 19.1 and 19.2). The intensity of risk factors reduction should depend on their cardiovascular risk (Table 19.3).

Table 19.1.1 • Estimation of 10 year CVD Points for MEN (Framingham Point Scores)

Points	Age, y	HDL-C	TG	SBP (not treated)	SBP (treated)	Smoker	Diabetes
-2		1.6+		<120			
-1		1.3–1.6					
0	30–34	1.2–<1.3	<4.2	120–129	<120	No	No
1		0.9–<1.2	4.2–5.2	130–139			
2	35–39	<0.9	5.2–6.3	140–159	120–129		
3			6.3–7.4	160+	130–139		Yes
4			>7.4		140–159	Yes	
5	40–44				160+		
6	45–49						
7							
8	50–54						
9							
10	55–59						
11	60–64						
12	65–69						
13							
14	70–74						
15	75+						
Points alloted							

Grand Total : _____ points

Table 19.1.2 • CVD Risk for Men

Total Points	10 year Risk %	Total Points	10 year Risk %
≤-3	<1	8	6.7
-2	1.1	9	7.9
-1	1.4	10	9.4
0	1.6	11	11.2
1	1.9	12	13.2
2	2.3	13	15.6
3	2.8	14	18.4
4	3.3	15	21.6
5	3.9	16	25.3
6	4.7	17	29.4
7	5.6	18+	>30

Table 19.2.1 • CVD Points for Women

Points	Age, y	HDL-C	TG	SBP (not treated)	SBP (treated)	Smoker	Diabetes
-3				<120			
-2		1.6+					
-1		1.3–1.6			<120		
0	30–34	1.2–<1.3	<4.2	120–129		No	No
1		0.9–<1.2	4.2–<5.2	130–139			
2	35–39	<0.9		140–149	120–129		
3			5.2–<6.3		130–139	Yes	
4	40–44		6.3–<7.4	150–159			Yes
5	45–49		>7.4	160+	140–149		
6					150–159		
7	50–54				160+		
8	55–59						
9	60–64						
10	65–69						
11	70–74						
12	75+						
Points alloted							

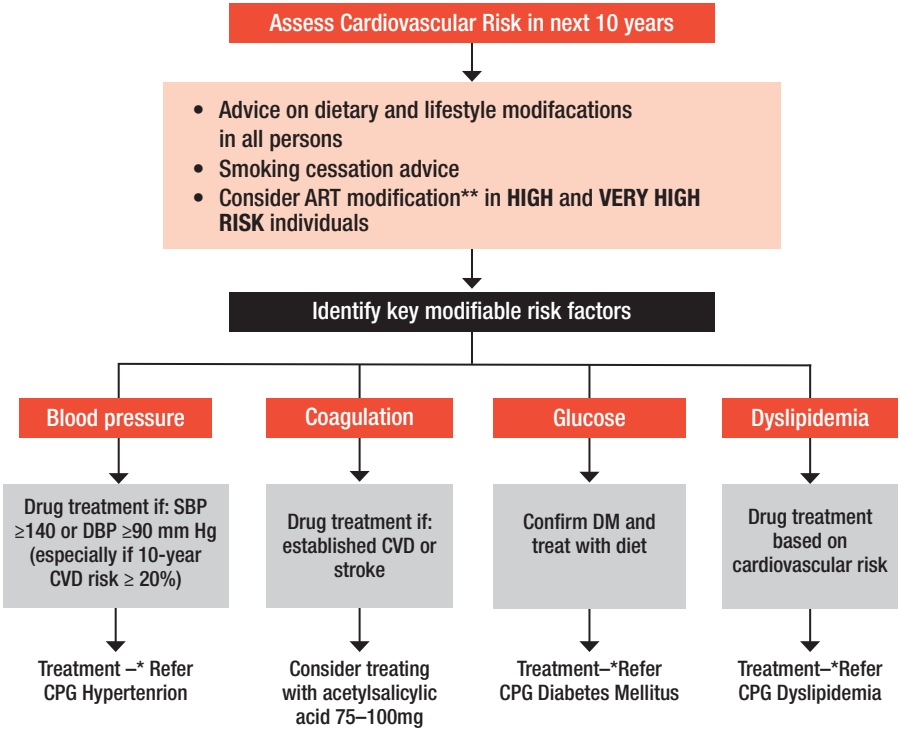
Grand Total : _____ points

Table 19.2.2 • CVD Risk for Women

Total Points	10 year Risk %	Total Points	10 year Risk %
≤-2	<1	10	6.3
-1	1.0	11	7.3
0	1.2	12	8.6
1	1.5	13	10.0
2	1.7	14	11.7
3	2.0	15	13.7
4	2.4	16	15.9
5	2.8	17	18.5
6	3.3	18	21.5
7	3.9	19	24.8
8	4.5	20	28.5
9	5.3	21+	>30

- **Very High Risk** individual are those with:
  - Established CVD
  - Diabetes with proteinuria or with a major risk factor such as smoking, hypertension or dyslipidaemia
  - CKD with GFR < 30 Ml/min^{-1}/1.73m^2 (≥ Stage 4)
- **High Risk** individuals include:
  - Diabetes without target organ damage
  - CKD with GFR ≥ 30–< 60 Ml/min^{-1}/1.73m^2 (Stage 3)
  - Very high levels of individual risk factors (LDL-C > 4.9 mmol/L, BP > 180/100 mmHg)
  - Multiple risk factors that confer a 10-year risk for CVD > 20% based on the Framingham General (FRS) CVD Risk Score
- **Intermediate (Moderate) Risk** Individuals:
  - Have a FRS-CVD score that confer a 10-year risk for CVD of 10-20%
- **Low Risk** Individuals:
  - Have a FRS-CVD score that confer a 10-year risk for CVD of <10%

(Adapted from Malaysia Clinical Practice Guidelines of Dyslipidemia 2017. Available at www.acadmed.org.my)



Refer to the latest Malaysian Clinical Practice Guidelines (CPG)

* Strategies for hypertensive, glycaemic and lipid control in patients with HIV infection are generally the same as for the general population. Refer to the latest Malaysian Clinical Practice Guidelines (CPG)

** Options for ART modification includes:
- Replace with NNRTI, INSTI or another PI/r known to cause less metabolic disturbances and/or lower CVD risks.
- Consider replacing ZDV or ABC with TDF or use an NRTI-sparing regimen.

Table 19.3 • Targets of Individual Risk Factors

Target of Individual Risk Factors			Grade of Recommendation Level of Evidence
Smoking	Complete Cessation		I, B
Physical Activity	Minimum 30 min/day, 5 days/week of moderate intensity PA (i.e. 150 min/week) or 15 min/day, 5 days/week of vigorous intensity PA (75 min/week) or a combination of both		I, B
Dyslipidemia	LDL-C: This should be the target of therapy. Treatment targets will depend on an individual's CVD Risk Classification (Table 3, pg 20)		
	Very High Risk: LDL-C goal: <1.8 mmol/L (or a reduction of at least 50% from baseline)		I, A
	High Risk: LDL-C goal: <2.6 mmol/L (or a reduction of at least 50% from baseline)		I, A
	Intermediate (Moderate) and Low Risk: LDL-C goal: <3.0 mmol/L		
BP*	<140/90 mmHg in most individuals <80 years of age		I, A
	<150/90 mmHg in individuals >80 years of age		I, A
Diabetes**	Pre-prandial blood sugar or fasting	4.4–7.0 mmol/L***	I, C
	Post-prandial blood sugar (90-120 mins after a meal)	4.4–8.5 mmol/L***	I, C
	A1c	≤ 6.5%***	I, A
	BP	≤135/75 mmHg	I, B
	LDL-C	≤ 2.6 mmol/L (the lower the better)	I, A
		≤ 1.8 mmol/L in diabetics with CVD	I, A
	HDL-C	> 1.0 mmol/L (males) > 1.2 mmol/L (males)	–
	Triglycerides	≤ 1.7 mmol/L	–
Overweight/ Obesity**	Weight loss	Aim for 5–10% in 6 months and maintain the weight in the next 1-2 years	1,A

(Adapted from Malaysian Clinical Practice Guidelines on Primary and Secondary Prevention of Cardiovascular Disease 2017. Available at www.acadmed.org.my)

19.2 Dyslipidemia

Studies have consistently shown a high prevalence of dyslipidemia among HIV-infected patients, with and without antiretroviral therapy. Indications for use of lipid lowering drugs in primary prevention of cardiovascular disease in HIV infection is the same as those of HIV-uninfected patients. LDL-C remains the primary target of therapy.

19.2.1 Effect of Antiretroviral Therapy on Lipid Level

- Use of Protease Inhibitors has been associated with development of dyslipidemia, although the effect will vary with the individual PI. Atazanavir-ritonavir is associated with more favourable lipid profile compared with lopinavir-ritonavir[6].
- Tenofovir and emtricitabine do not have an adverse effect on lipid profiles[7]. Consider replacing zidovudine or abacavir with tenofovir if 10-year CVD risk ≥20%.
- Integrase inhibitors – all agents in the integrase inhibitor class are associated with favourable lipid profiles

Table 19.5 • Effect of Antiretroviral Agents on Lipid Parameters

cART	Effect on Dyslipidemia	Comment
NRTI		
Zidovudine	↑↑	Significant increase in TC/LDL
Stavudine	↑↑	Significant increase in TC/TG
Abacavir	←→/↑	TC/HDL ratio unchanged
Tenofovir	↓	Reduction in LDL/TC
NNRTI		
Nevirapine	↓	Can increase HDL Level
Efavirenz	←→/↑	May increase lipid Level slightly
Etravirine	←→/↑	No significant changes
Protease inhibitor		
Lopinavir/ritonavir	←→/↑	Elevation of TC/TG frequent
Fosamprenavir/ritonavir	↑	Elevation of TC/TG
Atazanavir/ritonavir	←→	PI with best lipid profile
Darunavir/ritonavir	←→	Good lipid profile
Integrase inhibitor		
Raltegravir	←→	Low frequency of dyslipidemia
Chemokine receptor-5 antogonist		
Maraviroc	←→	No significant changes

HDL = high-density lipoprotein; LDL = low-density lipoprotein; NNRTI = non-nucleoside reverse transcriptase inhibitors; NRTI = nucleoside reverse transcriptase inhibitors; TC = total cholesterol; TG = triglyceride

19.2.2 Lipid Lowering Drugs

Statins are the lipid lowering drugs of choice, especially in patients with high LDL-C. Threshold for initiation of drug therapy and target LDL-C levels should be based on individual's cardiovascular risk (Table 19.6).

Table 19.6 • Target LDL-C Levels

Global Risk	LDL-C Levels to Initiate Drug Therapy (mmol/L)	Target LDL-C Levels (mmol/L)
Low CV Risk*	Clinical Judgement**	< 3.0
Intermedia (Moderate) CV Risk*	> 3.4**	< 3.0
High CV Risk • > 20% 10-year CVD risk • diabetes without target organ damage • CKD with GFR 30–<60 ML/min^{-1}/1.73m^2	> 2.6	**≤ 2.6 or a reduction of > 50% from baseline*** **
Very High CV Risk • established CVD • diabetes with proteinuria or with a major risk factor such as smoking, hypertension or dyslipidaemia • CKD with GFR < 30 ML/min^{-1}/1.73m^2 but not dialysis dependent)	> 1.8	**< 1.8 or a reduction of > 50% from baseline*** **

* Low and Moderate CV risk is assessed using the Framingham General CVD Risk Score
** After a therapeutic trial of 8-12 weeks of TLC and following discussion of the risk: benefit ratio of drug therapy with the patient
*** whichever results in a lower level of LDL-C

19.2.3 Suggested Statin Therapy

- Pravastatin has a good safety profile with limited drug interaction with ART. However, it is not as potent as other statins in reducing LDL cholesterol.
- Lovastatin and simvastatin should be avoided in patients on protease inhibitors.
- Rosuvastatin is a potent reducer of LDL-C with no substantial interactions with ART.
- Atorvastatin is also a reasonable option but warrant consideration for ART interaction. Lower doses of atorvastatin (10–20 mg) is recommended when used with ART in combination with cobicistat. This increases the effect of atorvastatin.

Table 19.7 • Statin Interactions With Antiretroviral Agents

Drug	Metabolism	PI	NNRTI
Lovastatin	CYP3A4	Contraindicated with PIs	Decreases lovostatin's AUC; thus, a higher lovastatin starting dose may be needed
Simvastatin	CYP3A4	Contraindicated with PIs	Acceptable with appropriate dosing Efavirenz and etravirine decrease simvastatin's AUC
Pravastatin	Partial hepatic (OATP1B1); partial urinary/ biliary excretion	Acceptable with appropriate dosing and monitoring; darunavir increase pravastatin's AUC	Acceptable with appropriate dosing and monitoring
Fluvastatin	CYP2C9, CYP3A4	Acceptable with appropriate dosing and monitoring; not recommended with nelfinavir	Acceptable with appropriate dosing and monitoring Etravirine may increase fluvastatin's AUC
Atorvastatin	CYP3A4	Use with causion. Do not coadminister with tipranavir/ritonavir	Acceptable with appropriate dosing and monitoring Efavirenz and etravirine decrease atorvastatin's AUC
Rosuvastatin	CYP2C9	Acceptable with appropriate dosing and monitoring; lopinavir/ritonavir and tipranavir/ritonavir increase rosuvastatin's AUC	Acceptable with appropriate dosing and monitoring
Pitavastatin	CYP2C9 glucuronidation	No significant interaction; mild decrease in pitavastatin's AUC with darunavir	No data on NNRTI

Adapted from Aberg et al
AUC = area under the curve; CYP = cytochrome; NNRTI = non-nucleoside reverse transcriptase inhibitors; OATP1B1 = Organic Anion Transporting Polypeptide 1B1/SLCO1B1.

(Aberg JA, Gallant JE, Ghanem KG, et al. Primary care guidelines for the management of persons infected with HIV: 2013 update by the HIV Medicine Association of the Infectious Diseases Society of America. Clin Infect Dis 2014;58:1-10)

19.2.4 Hypertriglyceridemia

- Treatment of hypertriglyceridemia in patients with HIV infection is the same as that in general population.
- Fenofibrates are preferred because there is no significant interaction with ART.

19.3 Diabetes Mellitus

A higher risk of insulin resistance and diabetes mellitus has been described in patients with HIV infection on ART compared with uninfected patients.[8] Associations between some ARTs and type 2 diabetes mellitus are more common with older ARTs such as stavudine, zidovudine, indinavir, and lopinavir and less common with tenofovir, emtricitabine, lamivudine, darunavir and atazanavir. Coinfection with Hepatitis C virus (HCV) also increases the risk of type 2 diabetes mellitus in people living with HIV[9].

Patients with HIV infection should be screened for diabetes at baseline and after initiation of ART. Of note, data are accumulating that Hba1c may underestimate glycemia in HIV-infected individuals[10]. Thus, HIV clinicians should consider that the Hba1c goal may need to be more stringent in HIV-infected patients, reflecting the underestimation of glycemia by Hba1c in HIV.

Special caution should be used when metformin is co-administered with dolutegravir, as dolutegravir increases metformin concentration. Thus, dose adjustment of metformin should be considered when both drugs are usedl[11].

A patient who develops diabetes while taking ARTs that is potentially diabetogenic, especially zidovudine, didanosine and first-generation PIs (lopinavir, indinavir), should be switched to a different ART regimen, if possible, with a safer metabolic profile such as tenofovir, atazanavir and dolutegravir[12].

Otherwise, diagnosis and management of diabetes mellitus for people living in HIV are generally the same as for the general population. Current national guidelines for the general population should serve as the guiding tool for treatment of diabetes in people living with HIV.

19.4 Hypertension

Hypertension is a known risk factors for cardiovascular disease. HIV infection may have higher rates of hypertension compared with uninfected patients. WHO recommends assessment for major non-communicable diseases such as hypertension, at HIV diagnosis or initiation of ART[13]. A blood pressure check should be performed at least annually[14]. Screening, diagnosis and management of hypertension in the HIV-infected patients are the same as those of for the general population.

Drug-drug interactions between antihypertensives and ARTs

- No interactions between thiazide diuretics like hydrochlorothiazide and ACE inhibitors and ARTs[15].
- Drug levels of calcium channel blockers (CCB) and beta blockers are increased in the presence of protease inhibitors (PIs) and decreased in the presence of non-nucleoside reverse transcriptase inhibitors (NNRTI). Dosage adjustment of the antihypertensive agent may be required[15].
- Drug levels of ARVs are not affected by CCB or beta blockers and no dose adjustment is required[15].

For additional drug-drug interactions and for more detailed pharmacokinetic interaction data and dosage adjustments, please refer to http://www.hiv-druginteractions.org (University of Liverpool).

Table 19.8 • Drug Interaction Table

Antihypertensive	TDF/ TAF	AZT	3TC	FTC	EFV	NVP	DTG	LPV/r	ATV/r	DRV/r
Hydrochlorothiazide										
amlodipine					↓	↓		↑	↑	↑
enalapril										
bisoprolol*					↓	↓		↑	↑	↑

* WHO Essential Medicines list includes atenolol, metoprolol, carvedilol as alternatives

No interaction

Potential interaction with increased or decrease levels of antihypertensives which may require dose adjustment. Drug levels of ARVs are not affected by calcium channel blockers or beta-blockers and no dose adjustment is required.

Caution should also be exercised when administering B blockers and PIs due to the risk of QT prolongation. **ECG monitoring is recommended.**

↑ Increase in antihypertensive drug level ↓ Decrease in antihypertensive drug level

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CHAPTER 20

VACCINATIONS FOR ADULTS LIVING WITH HIV

20.1 Introduction

This chapter provides recommendations on the use of vaccines in adults living with HIV. Compared to HIV-negative adults, HIV-positive adults are at increased risk of infection and higher risk of morbidity from exposure to vaccine-preventable infections. In addition, successful viral suppression and immune restoration with antiretroviral therapy (ART) has led to improved health and greater likelihood of HIV-positive adults to engage in travel or occupations that may expose them to vaccine-preventable infections. Recommendations on the use of vaccines in children living with HIV are not covered in this chapter. The authors suggest consultation with a pediatric infectious disease specialist for this group of patients.

Further reading on adult vaccinations against infections not covered in this chapter is available in the third edition of the 2020 Malaysian Guidelines for Adult Immunisation

20.2 General Principles

When considering the use of vaccines in HIV-positive adults, the following general principles apply:

1. Vaccines are less immunogenic with short-lived antibody response in HIV-positive persons compared to HIV-negative persons
2. Antibody responses are dependent on the immune status of the HIV-infected individual. Hence a person with higher CD4 count has better antibody response compared to a person with lower CD4 count
3. Administration of vaccine to HIV-positive persons after immune reconstitution and virologic suppression with ART is likely to elicit better antibody response
4. Non-replicating vaccines (e.g. inactivated, polysaccharide, conjugated and subunit vaccines, or virus-like particles) are safe to be used in HIV-positive persons. They are also safe for use in pregnancy and during breastfeeding if there are clear indications for its use[1]
5. Replicating or live vaccines, although traditionally contraindicated in HIV-infected persons, can be used in HIV-positive persons with good immunity. These vaccines should be given only after careful considerations of indications and benefits versus risks
6. Replicating or live vaccines are contraindicated in HIV-positive adults with CD4 count < 200 cells/μL. They are also contraindicated in pregnancy[1]

20.3 Malaysian Guideline on Adult Vaccination

The National immunisation schedule for Malaysia is primarily directed towards infants, children and adolescent. Adult immunization for groups who are at risk of contracting specific infections by virtue of occupational exposure, underlying diseases or travel is now widely practiced in Malaysia. During the CoVID-19 pandemic, adult vaccination gained widespread awareness following the government's directive to vaccinate all individuals including children and adolescents to curb COVID-19 infection.

The current practice on adult vaccination in Malaysia is guided by the Third Edition of the Clinical Practical Guideline for Adult Vaccination that was revised in 2020 .

Vaccine	Type	Replicating	Primary course	Indication	Remarks
CoVID19					
BCG	Live attenuated bacilli	Yes		Contraindicated	Has little or no effect in reducing tuberculosis in adults [WHO Euro]
Cholera	Inactivated + subunit	No	2 doses	See text (18.6)	
Diphtheria	Toxoid	No	1 dose	See text (18.7)	Combined as DTaP or DT
Hep A	Inactivated	No	2 – 3 doses	Non-immune, at risk	3 doses if CD4 < 350 cells/μL.
					See text (18.8)
Hep B	Subunit	No	3 – 4 doses	All non-immune	See text (18.9)
HiB	Conjugated	No	1 dose	At risk	Not recommended routinely for HIV-positive adults
HPV	Virus-like particles	No	3 doses	See text (18.11)	4vHPV or 9vHPV preferred
Influenza	Inactivated	No	1 dose	Annually	Quadrivalent preferred. Intranasal vaccine contraindicated
JE	Vero cell-derived inactivated	No	2 doses	See text (18.13)	In the National Immunisation Schedule for people living in Sarawak
Measles, Mumps, Rubella	Live attenuated	Yes	2 doses	All non-immune	Combine as MMR; CD4 >200 cells/μL
Meningococcus	Conjugated or recombinant protein	No	2 doses	See text (18.15)	Offered to pilgrims intending to perform the Haj
PCV	Conjugated (PCV-13) Polysaccharide (PCV-23)	No	1 dose	All, once	PCV-23 preferred in adults
Pertussis	Acellular multicomponent	No	1 dose	Pregnant women	Combined as DTaP
Polio (IPV)	Inactivated	No	3 doses	See text (18.17)	Oral polio vaccine contraindicated
Rabies	Cell-culture derived	No	3 doses	See text (18.18)	3 doses for pre-exposure prophylaxis 5 doses for post-exposure prophylaxis
Tetanus	Toxoid	No	1 dose	See text (18.7)	Combined as DTaP or DT or ATT
Typhoid	Polysaccharide	No	1 dose	See text (18.19)	Parenteral only. Oral live-attenuated vaccine contraindicated
Varicella	Live attenuated	Yes	2 doses	All non-immune	Not recommended by WHO but recommended by BHIVA in patients with CD4 > 200 cells/μL. Contraindicated in pregnant and breastfeeding women.
Yellow Fever	Live attenuated	Yes	1 dose	See text (18.20)	CD4 > 200 cells/μL

BCG = Bacillus Calmette-Guérin; Hep B = Hepatitis B; Hep A = Hepatitis A; DTaP = Diphtheria, Tetanus & acellular pertussis; HiB = Hemophilus influenza type B; MMR = Measles, Mumps, Rubella; MR = Measles, Rubella; JE = Japanese Encephalitis – only in Sarawak; HPV = Human Papillomavirus; ATT = Antitetanus toxoid; DT = diphtheria & tetanus; PCV = pneumococcal vaccine; IPV = Inactivated Poliovirus Vaccine

20.4 COVID-19 vaccination

PLHIV especially those with CD4 count < 350 cells/mm^2 or with additional underlying conditions are identified as one of the priority groups for vaccination in the early phase of COVID-19 vaccination in Malaysia. In 2022 , a second booster of COVID-19 vaccination was recommended to reduce the risk of severe illness progression due to variant strains.

Further information on COVID-19 vaccination in Malaysia can be obtained in the Clinical Guidelines On Covid-19 Vaccination In Malaysia 4th Edition published in October 2021.

Severely immunocompromised PLHIV who are not vaccinated due to adverse effects have been identified as priority group to receive dual monoclonal antibodies as pre-exposure prophylaxis against COVID-19. The dual monoclonal antibodies prevents SARS CoV-2 viral attachment and also entry into the cells.

PLHIV who fulfils following criteria can be given monoclonal antibody:

- Age more than 12
- Weighs more than 40 kg
- Not on ARV and CD4 T lymphocyte < 50 cells/mm^3
- Not able to be fully vaccinated with any available CoVID-19 vaccines due to severe adverse reaction to CoVID-19 vaccine and its components

The dual monoclonal antibodies available in Malaysia currently is Tixagevimab and Cilgavimab.

- Tixagevimab 150 mg and Cilgavimab150 mg is administered as two separate consecutive intramuscular injections
- No dosage adjustment is required in pregnant or lactating women, geriatrics or individuals with renal impairmen

20.5 BCG (Bacillus Calmette-Guérin)

The BCG vaccine is absolutely contraindicated in all HIV-positive adults regardless of CD4 cell count, viral load and ART use.[1] The BCG confers protection against disseminated and severe tuberculosis in children < 2 years but offers no added protection against tuberculosis in adults with HIV than those without HIV-infection.[3] There are case reports of disseminated BCG disease and fatal dissemination in HIV-positive persons with some occurring many years post-BCG administration.[4-11]

20.6 Diphtheria, Tetanus, Pertussis

Vaccine against diphtheria is commonly administered in combination with vaccines against pertussis and/or tetanus (Tdap or Td vaccines). These vaccines are administered to children according to the National Immunisation Schedule.[2] As a primary course, ATT, DT and DTaP may be administered to HIV-positive persons irrespective of their immune status and with the same schedule as per for HIV-negative persons.[16]

Tdap is recommended in all adults for whom 10 years or more have elapsed since completion of their primary series, or since their last booster dose. Booster dose of Td or ATT should be administered every 10 years thereafter due to waning protection over time. Repeat doses are not required if the schedule for the primary series or booster doses is delayed

20.7 Hepatitis A Virus (HAV)

Hepatitis A vaccine is highly immunogenic with > 95% protective antibodies production within 4 weeks with a single dose in HIV-negative persons. The seroconversion rate is lower (about 70%) in HIV-positive persons after two doses.[1] The HAV vaccine is well tolerated in HIV-positive persons with durable response after 5 years in those with high CD4 count.[18] It is safe and has no effect on HIV viral load or clinical progression of HIV infection.[19-22]

HAV vaccination is recommended if the PLHIV meets general indications and are at risk in the following:[14]

1. Chronic liver disease
2. Men who have sex with men (MSM)
3. Injecting and non-injecting drug users
4. Travelers to highly endemic areas for HAV infection (vaccine to be administered at least 2 weeks before travel)

5. Hemophiliacs
6. Household or sexual contacts of infected persons

HIV-positive persons with CD4 >350 cells/μL should receive a single dose with a booster 6 months later.[1] HIV-positive persons with CD4 <350 cells/μL should receive 3 doses at 0, 1 and 6 months to increase seroconversion activity and durability. Human immunoglobulin may be offered together with 1st dose of HAV vaccine, to be given within 14 days of exposure, in HIV-positive persons with CD4 <200 cells/μL in situations where there is significant exposure (e.g. from intimate contact).[1]

20.8 Hepatitis B Virus (HBV)

Risk of HBV infection and chronicity are increased in HIV-positive persons. Patients with HIV-HBV co-infections have increased rates of progression to liver cirrhosis and hepatocellular carcinoma and higher fatality compared to those with monoinfection.[23,24] Unlike HAV vaccine, the rate of seroconversion to HBV vaccine is strongly dependent on CD4 cell count and viral load.[25-27] HIV infection impairs seroconversion and reduces its protective duration.[28] Response rate is 87% in HIV-positive persons with CD4 >500 cells/μL and 33% in patients with CD4 between 200 – 500 cells/μL.[29] Strategies to improve responses include revaccination, higher doses of vaccine and more frequent administrations.[30-34]

HBV vaccination is indicated for the following groups of patients:[14]

1. MSM
2. Heterosexuals with multiple sexual partners
3. Sex workers
4. Sexual partners or household contacts of HBV carriers
5. Injecting drug users
6. Patients on hemodialysis
7. Health care workers
8. All non-immune HIV-positive persons[17]

Yeast-based Hepatitis B vaccine (e.g. Engerix B) should be administered at the conventional dose of 20 μg at 0, 1 and 6 months for patients with CD4 >500 cells/μL.[14] Some guidelines recommend doubling the vaccine dose to 40 μg in primary vaccine course.[1] In patients with CD4 between 200 – 500 cells/μL, an intensive schedule at 0, 1, 2 and 12 months has been recommended. Non-responders (absent HBsAb titer 4 weeks post primary course) should receive a booster dose or revaccinated with a new series using 40 μg.[14] Non-responders after 6 doses are considered susceptible to HBV and will need hepatitis B immunoglobulin following exposure to HBV.[14]

Vaccination should be delayed in patients with CD4 < 200 cells/μL. ART should be started, and vaccination offered once CD4 > 200 cells/μL.[14]

20.9 Human Papilloma Virus (HPV)

HPV is a common sexually transmitted disease which is acquired via direct contact involving skin and mucous membrane. HPV is a dominant cause of cancer worldwide. Over 200 HPV types has been identified and 12 HPV types are “high risk” including HPV-16 and HPV-18 which cause cervical, anal and head and neck cancers. “Low risk” HPV types are non oncogenic but cause HPV infections including anogenital warts. There is evidence suggesting that HIV acquisition is significantly associated with HPV infection.[78]

PLHIV have an increased risk and rate of acquisition, frequently carry multiple HPV types and are at increased risk of HPV related diseases and malignancies. HPV-related anogenital disease in PLHIV, despite effective ARV, is more prevalent compared to HIV negative people. HPV carriage rates and overall disease risk increases at lower CD4 cell counts.

Malaysia has implemented a National HPV vaccination program among 13 years old girls in government and private schools under the MOH School Health Unit Program in 2010. HPV vaccine is most efficacious in HPV-naïve individuals, if administered prior to being sexually active.

HPV vaccination is indicated for the following groups:

1. previously unvaccinated HIV-positive men and women aged up to 26 years.[14]
2. HIV-positive MSM aged up to 40 years old, regardless of CD4, viral load, and ART use.[1]

A history of genital warts, abnormal cytology, or positive HPV-DNA test should not preclude vaccination as these do not constitute evidence of past infections.[17] Vaccination in HIV-positive persons with CD4 < 200 cells/μL should be deferred until CD4 > 200 cells/μL with ART. HPV vaccines are contraindicated in pregnant women and those with hypersensitivity reaction to yeast.[36]

Three highly efficacious HPV vaccines directed against high-risk HPV types are currently available. Formulations of HPV vaccine include the 9-valent Types (9vHPV), the quadrivalent (4vHPV) and the bivalent (2vHPV) vaccines. All the vaccines are effective against the "high risk" HPV Type 16 and 18. Current evidence suggests that from the public health perspective, the three vaccines offer comparable immunogenicity, efficacy and effectiveness. The 9vHPV or 4vHPV vaccines are preferred as they also protect against genital warts. All three HPV vaccines have excellent safety profiles.

HPV vaccine is given as intramuscular deltoid region injections, dose of 0.5mL as a 2 dose schedule (0,6–12 months). In 2016, the 2 dose schedule recommendations replaced the previous 3-dose schedule for adolescent who started HPV vaccination before age 15 years and for adults with certain immunocompromised conditions.

If the first dose of any HPV vaccine given at age ≤ 15 years, three dose schedule is to be completed. Second dose is recommended 1-2 months after the first dose and the second dose is recommended six months after the first dose. (0, 1-2, 6 month schedule)

If a vaccination schedule is missed or interrupted, there is no need to repeat earlier doses. The recommended dose is based on age at administration of the first dose.

HPV vaccine can be co-administered with other non-live and live vaccines. Co-administration with a booster dose of tetanus-diphtheria vaccination should be considered in vaccination programmes.

20.10 Influenza

Antibody responses to inactivated influenza vaccine in HIV-positive persons are lower compared to HIV-negative persons.[39,40] The degree of response can be correlated to CD4 cell count and viral load.[41-44] Inactivated influenza vaccines are safe and well tolerated in HIV-positive persons. It is also safe in HIV-positive pregnant women.[45]

Influenza vaccine is recommended annually for all HIV-positive persons regardless of CD4 count or viral load. The quadrivalent inactivated injectable vaccine is preferred. Intranasal influenza vaccine, which is a live-attenuated vaccine, is contraindicated in HIV-positive persons.

20.11 Meningococcus

Neisseria meningitis is a common cause of meningitis with high mortality and permanent sequelae. Around 5–15% of asymptomatic adults carry the bacterium in the nasopharynx. Outbreaks has been associated with Hajj pilgrims, household contacts of returning pilgrims and clusters involving people living in dormitories. Although HIV-positive persons have an estimated 5–13 times higher risk for invasive meningococcal disease, the vaccine is not recommended routinely for HIV-positive persons in Malaysia.[52-54] Meningococcus vaccine is offered to pilgrims intending to perform the Hajj or Umrah.

Quadrivalent (ACWY) conjugate Meningococcus vaccine is available in Malaysia. It is administered as a two-dose schedule, administered 8 weeks apart.[1] Vaccinations should be considered for travelers to areas with high disease burden and among high-risk patients such as asplenic patients or those with complement deficiencies. A 5 yearly conjugate vaccine is recommended if still at risk of meningococcal exposure. The different conjugate vaccines can be used interchangeably for the booster doses.

20.12 Pneumococcal Vaccine

HIV-positive persons are at approximately 40-times higher risk of pneumococcal infection compared to HIV-negative persons.[55] Two types of vaccines against pneumococcus are available:

1. PPV-23 consisting of purified pneumococcal capsular polysaccharide from 23 serotypes, given as a single dose either subcutaneously or intramuscularly. It is highly immunogenic with persistent elevated antibody levels for at least 5 years, but may be less in HIV-positive persons
2. PCV-13 which is a 13-valent pneumococcal conjugate vaccine.

One dose of PPV-23 should be administered routinely, regardless of CD4 cell count or viral load in the following groups of people:[14]

1. Persons 65 years or older
2. HIV-positive adults with CD4 > 200 cells/μL and stable on ART
3. HIV-positive adults with CD4 < 200 cells/μL at increased risk of pneumococcal disease may be vaccinated. Once CD4 > 200 cells/μL on ART, revaccination should be considered
4. Revaccination should be considered after 5 years of the 1st vaccine

20.13 Varicella Zoster Virus (VZV)

HIV-positive persons, even when on effective ART, are 3 – 5 times higher risk of shingles compared to HIV-negative persons.[70-75] If they acquire chickenpox, they are more likely to have severe or fulminant disease.[76,77] Two varicella vaccines are available: Varilrix and Varivax. Both are live attenuated VZV vaccines and may cause vaccine-associated shingles in some recipients. **WHO does not recommend the administration of varicella vaccines for HIV-positive adults regardless of their immune status, viral load or ART use.[14]** The BHIVA guidelines recommend VZV vaccination in HIV-positive adults with CD4 >200 cells/μL and on effective ART, with negative or uncertain history of chickenpox or shingles. They should receive 2 doses of varicella vaccine administered 3 months apart.[1] Varicella vaccines are contraindicated in pregnant and breastfeeding women.[1] Reference : 3rd Edition 2020 Guidelines for Adult Vaccination

Immunisation for HIV Patients Based on CD4 Count

Vaccine	Cd4 count ≤ 200 cells/mm^3	Cd4 count >200 cells/mm^3
Hepatitis A[1]	R	R
Hepatitis B[2]	R	R
HiB	UI	UI
HPV[1]	R	R
Influenza (inactivated)	R	R
MMR	C	UI
Meningococcus[4]	R	R
Pneumococcus	R	R
(PCV13 and PPV23)[5]		
Rabie	UI	UI
Tetanus-Diptheria (Td)	UI	UI
Varicella[6]	C	UI
Yellow Fever[7]	C	UI
Zoster[8]	C	UI

R–recommended; C–contraindicated; UI–usual indication

1. Recommended for people who inject drugs (PWID), men who have sex with men (MSM), chronic hep B or C virus infections, haemophiliacs or those receiving clotting factor concentrates
2. For nonimmune (anti-HBs <10mIU/ml): 20 mcg as 4 dose series at 0, 1, 2, and 6 months. Better immune response in those with HIV viral load suppressed
3. Males and females through 26 years. 3 dose series at 0, 1-2, and 6 months.
4. 2 doses of MenACWY given ≥ 2 months apart and booster given every 5 years.
5. Previously unvaccinated: 1 dose of PVC13 followed by 1 dose of PPV23 >8 weeks later (preferably when CD4 count >200 cells/mm^3). Repeat PPV23 dose 5 years later. Previously vaccinated with PPV23, give PCV13 at >1 year later followed by PPV-23, 5 years after the previous dose. PCV13 can be given at any CD4 cell count. For PPV23 is it preferable to wait until CD4 count is > 200 cells/mm^3.
6. VZV seronegative and CD4 count >200. 2 doses 3 months apart. Discontinue antiherpetic medications (e.g. acyclovir) at the time of vaccination and for the next 4 weeks
7. In those with CD4 count >200 cells/mm^2, better immune response id shown in those with HIV viral load suppression*
8. Shown to be immunogenic in those with CD4 count >200 and suppressed HIV viral load[8]. Discontinue antitherpetic medications (e.g. acyclovir) at the time of vaccination and for the next 4 weeks

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