Malaysian Consensus Guidelines on Antiretroviral Therapy 2017 MINISTRY OF HEALTH MALAYSIA

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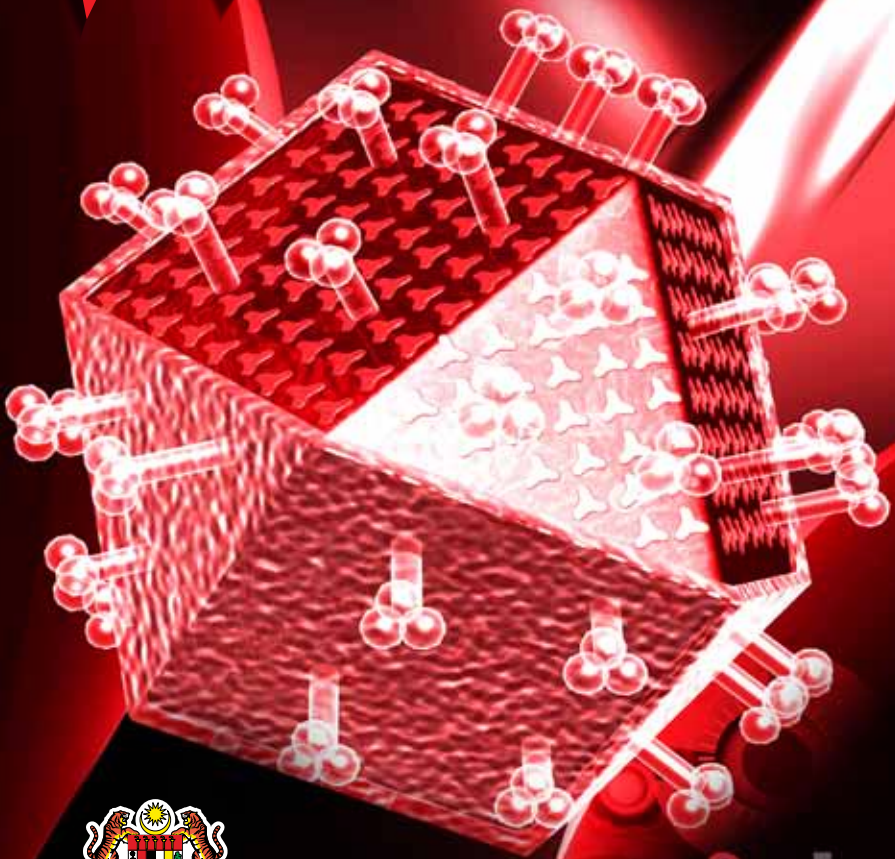

MINISTRY OF HEALTH MALAYSIA

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Abbreviations

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

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CHAPTER 1

INTRODUCTION

Since 1996, the management of Human Immune Deficiency Virus (HIV) infection has been revolutionized highly active antiretroviral therapy (HAART), usually consisting of three or more antiretroviral (ARV) drugs that act on different targets in the virus.1 HAART is synonymous with antiretroviral therapy (ART) and 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 drugs 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 2014 Guideline?

Relevant chapters have been reviewed and updated based on the current information and two new chapters about non-occupational postexposure prophylaxis (nPEP) and preexposure prophylaxis (PrEP) had been added.

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 those are available
4. Underlying medical diseases such as cardiovascular disease, diabetes mellitus, hyperlipidemia, 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. Reduction in complications associated with HIV / AIDS such as wasting syndrome, AIDS dementia and encephalopathy
7. Prevent HIV transmission to uninfected sexual partner and the unborn child
8. Prevent emergence of HIV drug resistance

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 to undetectable level at six months after initiation of treatment (undetectable is defined as VL < 20 copies/mL)

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 six classes of ARV drugs which target different phases in the HIV life cycle (see Table 1.0).

Table 1.0 • Antiretroviral Drugs in Malaysia

Class	Abbreviation
Nucleoside or nucleotide reverse transcriptase inhibitors (NRTI)	
Abacavir	ABC
Emtricitabine	FTC
Lamivudine	3TC
Stavudine	3TC
Tenofovir disoproxil fumarate	TDF
Zidovudine	AZT or ZDV
Non-nucleoside reverse transcriptase inhibitors (NNRTI)	
Efavirenz	EFV
Etravirine	ETV
Nevirapine	NVP
Rilpivirin	RPV
Protease Inhibitors (PI)	
Atazanavir	ATV
Darunavir	DRV
Lopinavir / ritonavir	LPV/r
Ritonavir	RTV
Integrase Inhibitors	
Raltegravir	RAL
Dolutegravir	DTG
CCR5 Antagonist	
Maraviroc	MVC
Fusion Inhibitor	
Enfuvirtide	T-20

1.5 Fixed Dose Combinations

Fixed dose combinations (FDC) are multiple ARV drugs combined into a single tablet (see Table 1.2). FDCs reduce pill burden and cost. Dosing simplification improves adherence and maintain durable virological suppression.[3,4]

Table 1.2 • Fixed Dose Combinations Registered in Malaysia

Fixed Dose Combinations	Brand name (eg.,)
Abacavir/Lamivudine (ABC/3TC)	Kivexa
Abacavir/Lamivudine/Zidovudine (ABC/3TC/AZT)	Trivizir
Lopinavir/Ritonavir (LPV/r)	Kaletra
Tenofovir disoproxil fumarate/emtricitabine (TDF/FTC)	Truvada, Tenvir-Em
Zidovudine/Lamivudine (AZT/3TC)	Combivir, Zovilam

REFERENCES

1. Moore RD, Chaisson RE. Natural history of HIV infection in the era of combination antiretroviral therapy. *AIDS*. 1996;13 (14): 1933–1942.
2. Palella FJ Jr, Delaney KM, Moorman AC et al. for HIV Outpatient Study Investigators. Declining morbidity and mortality among patients with advanced HIV infection. *N Engl J Med*. 1998; 338:853-860.
3. Stone VE, Hogan JW, Schuman P, et al. Antiretroviral regimen complexity, self-reported adherence, and HIV patients' understanding of their regimens: survey of women in the HER study. *J Acquir Immune Defic Syndr*. 2001; 28(2):124-131.
4. Stone VE, Jordan J, Tolson J, Miller R, Pilon T. Perspectives on adherence and simplicity for HIV infected patients on antiretroviral therapy: self-report of the relative importance of multiple attributes of highly active antiretroviral therapy (HAART) regimens in predicting adherence. *J Acquir Immune Defic Syndr*. 2004; 36(3):808-816.

CHAPTER 2

ASSESSMENT OF ADULTS WITH HIV INFECTION

All adults with HIV infection should have a complete history, physical examination, and baseline laboratory evaluation and counselling about the HIV infection[1].

1. A thorough history for all patients with HIV infection.
2. Ensure patient understands HIV infection and its mode of transmission
3. Obtain baseline historical and laboratory data
4. A complete physical examination to look for signs related to AIDS and opportunistic infections.
5. Look for evidence of opportunistic infections, HIV-related illnesses and evaluation for possible sexually transmitted diseases
6. Laboratory testing for initial evaluation AND monitoring during follow-up.
7. Confirm the diagnosis of HIV infection
8. Obtain baseline laboratory data
9. To initiate 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 a HIV Positive Patient[3]

	Symptoms / Components	Significance
History of Presenting Complaint	Fever, Cough, Dyspneoa, Diarrheoa, constitutional symptoms. urethral discharge, genital ulcers/ other skin lesions suggestive of sexually transmitted diseases	Diagnosis of opportunistic infections.
	Lethargy, weakness, weight loss loss, forgetfulness.	Symptoms of AIDS
Drug History	Current medications & dosage Alternative medications Smoking & Alcohol Recreational drugs use Drug addiction Drug addiction	Allergy Potential drug interaction Route: IV, oral etc.
Past & Current Medical History	TB, hepatitis, herpes, varicella, (Syphilis, gonorrheoa, Chlamydia) DM, IHD, HPT, Renal disorder, Dyslipidaemia.	Risk of worsening condition due to ARVs.

	Symptoms / Components	Significance
	Treatment received or completed for the above. Vaccinations Last negative HIV test.	
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	PMTCT prophylaxis. Transmission prevention measures.

Table 2.1 • Important Laboratory Investigations[2]

Evaluation	Investigations	Specific Tests	Entry to Care	Pre-HAART	At Follow-up on HAART	Comments
HIV Disease	All referred cases of HIV infection need a confirmatory test.					
	Plasma HIV RNA	HIV viral load	See comment	x	Every 4 to 6 months after initiation of ART. Annually if stable.	Not for routine baseline if resources are limited.
	CD4		√	√	Refer section 2.1	
Co-infections	Syphilis serology	VDRL/RPR/TPHA	√	X	Annual screening if at risk	Consider more frequent
	Hep A Serology for "at risk group", if facility available for testing)	Hep A Ig G	At risk group			Risk group: MSM Vaccination if non immune
	Hep B Serology	Hep. Bs Ag (HbsAg) Anti-Hep. Bs (HbsAb)	√	X	Annual screening if at risk	Vaccinate if non-immune. Consider testing for Anti-Hep B core antibody (HBc Ab total) if Hep Bs Ag negative and liver function abnormal. Measure HCV RNA if HCV antibody positive or acute infection suspected.
	Hep C Serology	HCV Antibody	√	X	Annual screening if at risk	
CXR			√	X	When clinically indicated	To look for active TB (consideration for IPT).

Evaluation	Investigations	Specific Tests	Entry to Care	Pre-HAART	At Follow-up on HAART	Comments
Hematology	FBC		√	√	Every 4 to 6 months (only if patient is on AZT or symptomatic)	If on AZT – before initiation and at week–4, 8 & 12 or symptomatic
CVS	ECG		√	If on PIs	When clinically indicated.	If patient has other risk factors for IHD
Metabolic	Fasting lipid profile		√	X	Every 6 to 12 months	EFV, NRTIs, PIs (with the exception of unboosted atazanavir), can cause insulin resistance and dyslipidaemia.
	Fasting blood sugar		√	X	Annually if initial screening results are normal 3–6 monthly	
Liver	ALP, AST ALT, Bilirubin, Albumin		√	√	Every 4 to 6 months	NRTI and NNRTI drugs can cause hepatotoxicity. If on NVP, ALT need to be monitored more frequently; at baseline, 2, 4, 12 weeks and then every 3-6 months Obtain ALT in patients with new onset of rash
Renal	Renal function test/ eGFR		√	√	At week 4, 8 & 12 upon initiation of Tenofovir (TDF) 4 to 6 monthly 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
	Dipstick		√	If clinically indicated		
Others	Serum Lactate		X	X	As clinically indicated	Lactic acidosis is a rare but severe complication of NRTI therapy caused by mitochondrial dysfunction.
	Cervical PAP Smear for women	Pap smear	√		Annually, if the results of the 3 consecutive Pap tests are normal, follow up Pap tests should be every 3 years [3]	

2.1 Monitoring While on Antiretroviral Therapy (refer Table 2.1)

CD4 Count:

Successful therapy is defined as an increment in CD4 cell counts that averages 50 –150 cells/mm per year until a threshold is reached. However, some patients may experience a slower increase of CD4+ T cell counts particularly when anti-retroviral therapy (ART) were initiated at very low baseline CD4 count levels.[1]

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

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

Once the HIV viral load is suppressed and CD4 counts >350cells/mm^3 on 2 occasions 6 months apart, further repeat of CD4 count is not needed.[2] (Unless treatment failure is suspected)

HIV Viral Load

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

HIV Viral Load is Recommended of ART :

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

**subjected to resource availability

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 20 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 (see also "Initial assessment of treatment failure" in chapter 4).

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 need to be complemented by assessment of treatment side effects and adherence.

2.2 Co-Trimoxazole Preventive Prophylaxis (Refer Table 2.2)

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

Table 2.2 • PJP Prophylaxis

When To Start	What To Start	When To Stop
1. CD4 count of <200/µL or CD4 percentage of <14% 2. Oropharyngeal candidiasis 3. Opportunistic infections / AIDS defining illness 4. Patient who has completed successful treatment for PCP	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

Co-Trimoxazole in Pregnant / Lactating Women

Women who fulfill 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 drugs and relatively contraindicated in severe liver disease, severe anemia or severe pancytopenia. As an alternative, dapsone at a dose of 100 mg daily may be used.

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

Note: Co-trimoxazole oral suspension contains 200 mg SMX + 40 mg TMP per 5 ml
(Adopted from Consensus Guidelines on antiretroviral therapy 2014)

REFERENCES

1. Aberg JA, Gallant JE, Ghanem KG, Emmanuel P, Zingman BS, Horberg MA. Primary care guidelines for the management of persons infected with HIV. CID. 2014; 58(1):e1.
2. Guidelines on the routine investigation and monitoring of HIV-1-infected adults Consultation Draft. *British HIV Association*; 2016.
3. Panel on Opportunistic Infections in HIV-Infected Adults and Adolescents. Guidelines for the prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from the Centers for Disease Control and Prevention, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America; 2017

CHAPTER 3

OPTIMIZING CARE AND MAXIMIZING BENEFITS OF ART

First line HAART 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. PLWH should be given opportunity in making decisions about their treatment. Studies showed that good relationship and good communication skills between clinician and PLWH are associated with better treatment outcome.

3.1 Pre ART Counselling

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

Before prescribing ART, clinician should assess individuals:

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

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

3.2 ART Counseling

Currently, first line HAART offers the best opportunity for effective viral suppression and immune recovery. It also improves mortality as it improves AIDS

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

3.3 Adherence to ART

ART adherence is the key to successful HIV treatment

ART adherence is the key to successful HIV treatment. Current data shows that to maintain successful viral suppression, 95% or more adherences to ART is required. Interventions to improve adherence are most likely to be successful when they are comprehensive and tailored to individual's socio-demographics background and behavioural characteristic.

Specific group at risk of poor adherence includes:

- Poor family support
- Intravenous drug users
- Adolescence and
- 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' • 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	a) Preferably once a day regime
Identify potential barriers to adherence	• Psychosocial issues (e.g. housing problems, legal issues, disrupted family) • Active substance abuse or at high risk of relapse • Low literacy • Busy daily schedule and/or travel away from home • Nondisclosure of HIV diagnosis – the need of 'treatment buddy' • Scepticism about ART • Lack of continuous access to medication

Strategies	Examples
Provide resources for the patient	• Referrals for mental health and/or substance abuse treatment • Continuous pill supply - e.g. SPUB "Sistem Pendispensan Ubat Bersepadu" to nearest government clinic, postage of medication to patient's home, pre-packaged medications – 'drive-through counter' • Pillboxes
Assess adherence at every clinic visit	• Use a simple checklist that the patient can complete in the waiting room • Ensure that other members of the health care team also assess adherence • Ask the patient open-ended questions (e.g., In the last 3 days, please tell me how you took your medicines)
Identify the type of non-adherence	• Failure to fill the prescription(s) • Failure to take the right dose(s) at the right time(s)
Identify reasons for non-adherence	• Adverse effects from medications • Complexity of regimen (pill burden, dosing frequency, etc.) • Difficulty swallowing large pills • Forgetfulness • Failure to understand dosing instructions • Inadequate understanding of drug resistance and its relationship to adherence • Pill fatigue • Other potential barriers

3.4 Increase Retention and Linkage to Care

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

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

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

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

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

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

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

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

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

Linkage to Care • Step 4 Track Referrals

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

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

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

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

REFERENCES

1 Arnsten JH, Demas PA, Farzadegan H, et al. Antiretroviral therapy adherence and viral suppression in HIV-infected drug users: comparison of self-report and electronic monitoring. *Clin Infect Dis.* 2001 Oct 15;33(8):1417-1423

2. Chesney MA. The elusive gold standard. Future perspectives for HIV adherence assessment and intervention. *J Acquir Immune DeficSyndr.* Dec 1 2006; 43(Suppl 1):S149-155.

3. Christian Pardier, Laurence Bentz, Bruno Spire, et al. Efficacy of an educational and counselling intervention on adherence to Highly active antiretroviral therapy: French Prospective Controlled Study. *HIV Clin Trials.* 2003; 4(2):121–131

4. WHO guideline on HIV treatment 2015

5. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection Recommendations for a public health approach. June2013

6. Guidelines for the treatment of HIV-1-positive adults with antiretroviral therapy. British HIV Association, 2012

7. SS Lee, Justin CY WU, Ka-Hing Wong. Hong Kong HIV manual, 2007.

8. Self-report measures of antiretroviral therapy adherence: A review with recommendations for HIV research and clinical management. *AIDS Behav.* 2006 May;10(3):227-245

9. Simoni JM, Kurth AE, Pearson CR, Pantalone DW, Merrill JO, Frick PA. Self-report measures of Antiretroviral therapy adherence: A review with recommendations for HIV research and clinical management. *AIDs Behav.* May 2006; 10(3):227-245.

10. Raboud J, Li M, Walmsley S, et al. Once daily dosing improves adherence to antiretroviral therapy. *AIDS Behav.* 2011 Oct; 15(7):1397-1409.

11. Swaziland Ministry of Health. Patient Linkage, retention and follow up in HIV care. Swaziland, 2012.

12. Connecting HIV Infected Patients to Care: A Review of Best Practices, the American Academy of HIV Medicine, 2009

CHAPTER 4

FACTORS TO CONSIDER BEFORE INITIATING ANTIRETROVIRAL THERAPY (ART)

Antiretroviral therapy (ART) is recommended for all HIV-infected individuals, regardless of CD4 count, to reduce the morbidity and mortality associated with HIV infection. It is also to prevent HIV transmission. Summary of recommendation is shown in Table 4.0 below.

Table 4.0 • Factors to consider before starting ART for individuals without OI [1,2,3,4]

Target Population	Specific Recommendations
Adults (>18years)	**All HIV-infected individuals, regardless of CD4 count** **As a priority, ART should be initiated in :** • All adults with severe or advanced HIV clinical disease (WHO clinical stage 3 or 4) • Individuals with CD4 count ≤350 cells/mm^3 • HIV-associated nephropathy (HIVAN) • HIV/Hepatitis B virus co-infection • HIV/Hepatitis C virus co-infection • All pregnant ladies infected with HIV

4.1 Factors to Start ART in Individuals with Opportunistic Infections (OIs)

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

This guideline recommends clinical assessment at the end of 2 weeks of OI therapy. If patient is stable and has improved with OI treatment, initiation of ART can be considered.[3]

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.

However, in the following conditions, the timing of initiation of ART varies according to specific circumstances.

1. Tuberculosis[5]

ART is recommended in all HIV-infected persons with TB.

For ART-naive patients, ART should be started within 2 weeks when the CD4 count is <50 cells/mm^3 and by 8 to 12 weeks for all others.

In patients with TB meningitis and low CD4 cell counts, early ART may pose a risk that calls for careful monitoring and consultation with experts.

2. Cryptococcal Meningitis

Delay initiation of ART at least until after completion of antifungal induction therapy (the first 2 weeks) and possibly until the total induction/consolidation phase (10 weeks) has been completed. If effective ART is to begin prior to 10 weeks, the treating physicians should be prepared to aggressively address complications caused by Immune Reconstitution Syndrome (IRIS), such as elevated intracranial pressure (ICP).

Delay in ART may be particularly important in those with evidence of increased intracranial pressure or in those with low CSF white blood cell counts.

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.

REFERENCES

1. Guidelines on when to start anti-retroviral therapy and pre exposure prophylaxis for HIV. WHO; 2015.
2. Lundgren JD, Babiker AG, Gordin F, et al. Initiation of antiretroviral therapy in early asymptomatic HIV infection. *N Engl J Med.* 2015;373(9):795-807.
3. Cohen MS, Chen YQ, McCauley M, et al. Prevention of HIV-1 Infection with early antiretroviral therapy. *N Engl J Med.* 2011; 365(6):493-505.
4. The TEMPRANO ANRS 12136 Study Group. A trial of early antiretrovirals and Isoniazid preventive therapy in Africa. *N Engl J Med.* 2015;373(9):808-822.
5. Panel on Opportunistic Infections in HIV-Infected Adults and Adolescents. Guidelines for the prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from the Centers for Disease Control and Prevention, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America; 2013.

PRINCIPLE OF SELECTING FIRST LINE ART

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

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

5.1 Preferred and Alternative Options for First Line ART

2 NRTI+1 NNRTIs are the preferred option (see Table 5.0)

Table 5.0 • Preferred and Alternative ART Options

Preferred first line ART	Alternative regimes
TDF + FTC + EFV	AZT + 3TC + EFV (or NVP) ABC + 3TC + EFV (or NVP) TDF + FTC + NVP
TDF + FTC + Raltegravir TDF + FTC + Dolutegravir (if intolerant to NNRTI)	TDF + FTC + ATV/r TDF + FTC + LPV/r

5.2 Considerations Prior to Starting Treatment

5.2.1 NRTI

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. [1] The use of D4T is discouraged. For patients who are started on D4T, they should be switched to TDF or AZT after the first 6 months to avoid its long term adverse effects.

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

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

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

5.2.2 NNRTI

NVP and EFV have comparable clinical efficacy when used in combination ART. However, NVP is associated with higher risk of rash, Steven-Johnson Syndrome and hepatotoxcity compared to EFV.[5] In case of severe hepatotoxicity or skin reactions, NVP should be permanently discontinued. NVP must be avoided in women with CD4 count >250 cells/mm^3 and men with baseline CD 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.[3] EFV should be avoided in patients with severe psychiatric illness and in those whose daily functional status is affected by its side effects.

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, the backbone NRTIs should be continued for another 2 weeks before stopping all drugs.

5.2.3 INSTI and PI/r

Integrase strand transfer inhibitors (INSTI) or protease inhibitors (PI) may be considered as the third agent in first line ART regime if the patient is unable to tolerate the side effects of NNRTI. Patients who are unable to tolerate ART or develop adverse reactions to ART should be referred to infectious disease physicians.

REFERENCES

1. Campbell TB, Smeaton LM, Kumarasamy N, et al. Efficacy and safety of three antiretroviral regimens for initial treatment of HIV-1: a randomized clinical trial in diverse multinational settings. *PLos Med.* 2012; 9(8):e1001290.
2. Lucas GM, Ross MJ, Stock PG, Shlipak MG, et al. Clinical practice guideline for the management of chronic kidney disease in patients infected with HIV: 2014 update by the HIV Medicine Association of the Infectious Diseases Society of America. *Clinical Infectious Diseases.* 2014;17:1-43.
3. World Health Organization. Antiretroviral therapy for HIV infection in adults and adolescents: recommendations for a public health approach; 2010 revision.
4. Churchill D, Waters L, Ahmed N, et al. BHIVA guidelines for the treatment of HIV-1-positive adults with antiretroviral therapy; 2015.
5. Van Leth F, Phanuphak P, Ruxrungtham K, et al. Comparison of first-line antiretroviral therapy with regimens including nevirapine, efavirenz, or both drugs, plus stavudine and lamivudine: a randomised open-label trial, the 2NN Study. *The Lancet.* 2004;363(9417):1253-63.

MANAGEMENT OF TREATMENT FAILURE: AFTER FIRST LINE THERAPY

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

Successful virological suppression is defined as having a sustained viral load that is undetectable (e.g. viral load <20 copies/mL where 20 is the lower limit of viral load detection)

6.1 Viral "Blips"

Defined as isolated transient rises in viral load to above detectable level while on treatment after having achieved prior viral suppression and is followed by re-suppression. The levels generally do not exceed 200 copies/mL. It may reflect technical variations in laboratory assay performance, or biological events associated with viral replication (immunization, other viral infection). Isolated "blips" are not associated with subsequent virologic failure, but frequent episodes or higher viral loads, increase the risk of failure in the future. These patients should be assessed for possible causes of treatment failure.

6.2 Low Level Viremia

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

6.3 Virologic Failure

The viral load level to define virologic failure is not fully agreed on worldwide. WHO defines virologic failure as either an incomplete virologic response which is a failure to achieve HIV viral load <1000 copies/ml 4–6 months after starting therapy or a virologic rebound where after previous virologic suppression, there is a persistent HIV viral load to >1000 copies/mL while on the same regiment.

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

6.4 Assessment of Treatment Failure

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

Factors that Increase the Risk of Treatment Failure Include:

1. Previous ARV history using less potent regimens
2. Higher baseline HIV RNA level
3. Lower pre-treatment or nadir CD4 T-cell count
4. Prior AIDS diagnosis
5. Co-morbidities (e.g., depression, active substance use)
6. Presence of drug-resistant virus at baseline
7. Prior treatment failure, with development of drug resistance or cross resistance
8. Incomplete medication adherence and missed clinic appointments
9. Drug side effects and toxicity
10. Suboptimal pharmacokinetics (variable absorption, metabolism,food/fasting requirements, adverse drug-drug interactions with concomitant medications)

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

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

I. Thorough Review of the Patient's Medical History:

1. Change in HIV RNA and CD4 T-cell count over time
2. Occurrence of HIV-related clinical events
3. Antiretroviral treatment history
4. Results of prior resistance testing (if any)
5. Factors potentially contributing to reduced plasma drug levels such as:
   - **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)
   - **Incorrect dosing / frequency**
   - **Drug intolerance; management strategies include:**
     – Using symptomatic treatment (e.g., antiemetics, antidiarrheals);
     – Changing one drug to another within the same drug class, if needed (e.g., change to TDF or ABC for AZT-related gastrointestinal symptoms or anemia; change to NVP for EFV-related central nervous system symptoms)
     – changing drug classes (e.g., from an NNRTI to a PI if necessary)
   - **Pharmacokinetics**
     – Food/fasting requirements
     – Adverse drug-drug interactions with concomitant medications
   - **Co-morbidities** (including substance use)

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

6.4 Clinical Scenarios in Detectable Viral Loads.

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

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

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

4. **Viral Load Persistently >1,000 copies/mL and no resistance testing available.**
   Closely assess if the patient has been adherent for the last 4-6 months prior to the recent viral load test. Collaborate this history with next of kin if possible or relevant. If adherence is very likely, consider this as treatment failure due to resistance. In patients who are failing on the first line regime of NRTI + NNRTI, a resistance test is usually unnecessary. The resistance profile can be predicted and the second regime recommended is as expressed in Table 6.0

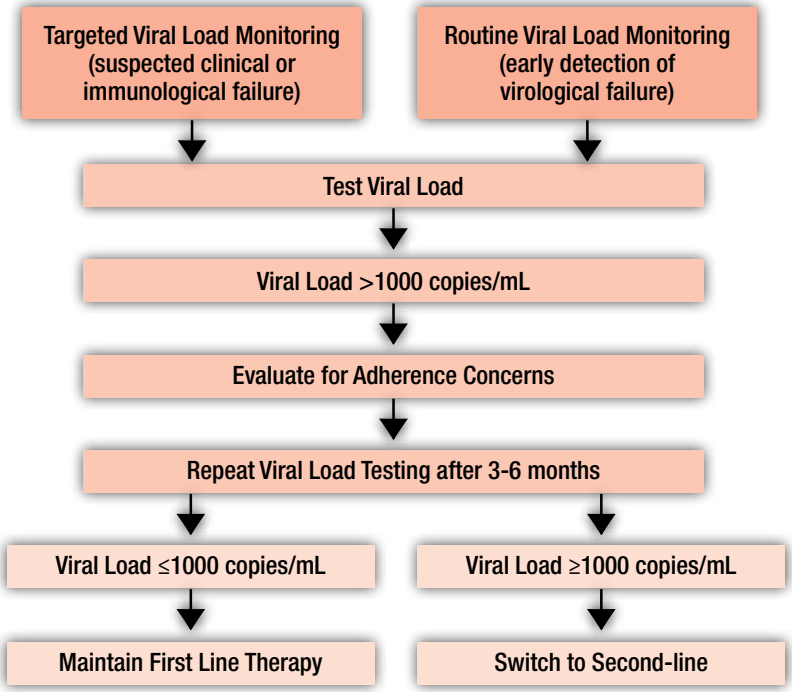
6.5 General Principles of Changing Therapy

- The new regimen should be designed based on drug history, past and current resistance test results to identify fully active agents, and/or to use antiretroviral drugs with new mechanisms of action if available.
- Ideally the new regimen should consist of at least 2, and preferably 3 fully active agents from at least one new class[5]
- In general, adding a single, fully active antiretroviral drug in a new regimen is not recommended because of the risk of development of rapid resistance to that single drug.

When to Switch

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

Fig 6.1 • Viral Load Testing Strategies to Detect or Confirm Treatment Failure and Switch ART Regimen in Adults and Adolescents



Adapted from WHO Consolidated ARV guidelines 2013

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

Choice of Second Line Regimes for Treatment Failures (refer table 6.0)
When the current first line regimes based on NNRTI and 2 NRTI (usually 3TC with AZT, d4T or TDF) fails, predicted resistance will be towards 3TC(M184V/I) and NNRTIs (Y181C/I/V,K103N). The number of thymidine analogue mutations (TAMs) selected by AZT/d4T will depend on how long the patient is maintained on the failing regime and the viral load at the time of switch.

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

Table 6.0 • Recommended Second Line Regime[1]

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

- *ABC may be used as potential back-up options in special circumstances (e.g. concomitant renal failure that precludes use of TDF or a past history of anemia precluding use of AZT).
- *3TC should be continued in second line regimes even though there is a strong likelihood of 3TC resistant mutations when the 1st line regimes fail. This is because the continued presence of the 3TC resistant mutation (M184V/I) confers a fitness toll on the HIV virus.
- ** TDF should not be discontinued in the second line regime in patients with underlying Hepatitis B as this can lead to flares in hepatitis.
- ***Lopinavir/Ritonovir (Kaletra™) and Raltegravir combination has been proven in one randomized trial to be as efficacious as standard second line regime consisting of 2 optimized NRTIs + 1 PI/r.
- Etravirine is a second generation NNRTI which has limited cross class-resistance and would be an option as a replacement for the NNRTI component of the regime. However this drug should only be considered in early treatment failure and would require prior HIV resistant testing while on the failing first line therapy.
- Raltegravir/Dolutegravir may be considered as a PI substitute if there is no PI option and HIV resistant testing affords a strong NRTI back bone.

6.6 Treatment-Experienced Patients with Limited or No Therapeutic Options

For extensively treatment experienced patients with limited or no options, maintaining a CD4 above 200 becomes the main focus. Viral load of up to 20 000 copies/mL may be acceptable in this group of patients.

In a failing patient with no other ART option, the decision whether to continue the failing regime or not will be based on cost and side effect of the drugs in the failing regime. If the patient is currently on therapy, continuing the failing regime rather than stopping it has been shown to be beneficial provided that the patient has not developed any side effects to the drugs and is clinically well. This has to be balanced with the fact that there is accumulation of mutations in the long term (as early as 1 year) which may negatively impact future treatment options should they become available. Hence if a potentially viable regime should become available, it must be commenced as soon as possible. Discussion with an ID physician is strongly encouraged in the management for these patients.

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

6.7 Viral Resistance Testing

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

If available, they should be performed in the following circumstances:

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

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

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

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

REFERENCES

1. Consolidated Guidelines on the use of Antiretroviral Drugs For Treating and Preventing HIV infection: Recommendation for a public health approach. *WHO*, 2013.
2. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services USA, 2013.
3. Campbell TB, Shulman NS, Johnson SC et al. Antiviral activity of lamivudine in salvage therapy for multidrug-resistant HIV-1 infection. CID 2005;41(2):236-42.
4. Durant J, Clevenbergh P, Halfon P, et al. Drug-resistance genotyping in HIV-1 therapy: the VIRAD APT randomised controlled trial. *The Lancet* 1999; 353(9171):2195-99.
5. Meynard JL, Vray M, Morand-Joubert L, et al. Phenotypic or genotypic resistance testing for choosing antiretroviral therapy after treatment failure: a randomized trial. *AIDS* 2002; 16(5):727-36.
6. Paton N, Kityo C, Hoppe A, et al. Assessment of second-line antiretroviral regimens for HIV therapy in Africa. *N Engl J Med* 2014; 371:234–247.

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]. ART must be started in all pregnant mothers who are HIV+ regardless of CD4 count.

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

Table 7.0 • Presenting CD4 and Timing of ART Initiation

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

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

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

7.2 Women Who are Stable on ART before Pregnancy

In general, the existing ART is to be continued throughout pregnancy and after delivery. Special effort must be made to determine the current CD4 and viral load during the early stages of pregnancy. Consultation with an ID physician is strongly recommended if the patient is experiencing virological failure.

7.3 Agents Used for PMTCT

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

Table 7.1 • Choice of ART Combinations

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

[a] In the past EFV was considered a Category D drug and contraindicated in the first trimester of pregnancy. However, there is now good level safety evidence to recommend it as the preferred NNRTI even in the first trimester[4].

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

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

7.4 Mode of Delivery

Pre-labour Elective Caesarean Section (PLCS) has been proven to further reduce the risk of transmission.[6,7] The decision between performing PLCS or allowing spontaneous vaginal delivery (SVD) is based 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.

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

Table 7.2 • 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 or unknown viral load	PLCS

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

7.5 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. Current evidence suggests that intrapartum IV AZT has no additional benefit in prevention of vertical transmission in pregnant women on ART with viral load ≤1000 copies/mL during late pregnancy and near delivery[9].

7.6 Women Presenting in Labour with No Prior ART Exposure

Intravenous (IV) AZT should be given immediately in 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 as the preferred 3rd agent because it rapidly crosses the placenta. If Raltegravir is not available, NVP or EFV should be used. After delivery, the ART can be switched to recommended first line ART regimen for non-pregnant patients.

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

7.7 Women Presenting with Spontaneous Rupture of Membrane (ROM)

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

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

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

7.8 Breast-Feeding

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

REFERENCES

1. Warszawski J, Tubiana R, Le Chenadec J, et al. Mother-to-child HIV transmission despite antiretroviral therapy in the ANRS French Perinatal Cohort. *AIDS*. Jan 11 2008;22(2):289-299.
2. Isabella No 'brega, Ana Gabriela Travassos, Tatiana Haguihara, Fa 'bio Amorim, and Carlos Brites. Short Communication: Use of Raltegravir in Late-Presenting HIV-Infected Pregnant Women. *AIDS Research and Human Retroviruses* Volume 29, Number 11, 2013.
3. Westling K, Pettersson K, Kaldma A, Naver L. Rapid decline in HIV viral load when introducing Raltegravir containing antiretroviral treatment late in pregnancy. *AIDS Patient Care STDS*. 2012; 714- 717.
4. Ford N, Calmy A, Mofenson L. Safety of efavirenz in the first trimester of pregnancy: an update systematic review and meta-analysis. *AIDS* 2011; 25: 2301– 2304.
5. Ford N, Calmy A, Andrieux-Meyer I et al. Adverse events associated with nevirapine use in pregnancy: a systematic review and meta-analysis. *AIDS* 2013; 27: 1135–1143.
6. European Mode of Delivery Collaboration. Elective caesarean-section versus vaginal delivery in prevention of vertical HIV-1 transmission: a randomised clinical trial. *Lancet*. Mar 27, 1999;353(9158):1035-1039.
7. International Perinatal HIVG. Duration of ruptured membranes and vertical transmission of HIV-1: a meta-analysis from 15 prospective cohort studies. *AIDS*. 2001;15(3):357-368.
8. Garcia PM, Kalish LA, Pitt J, et al. Maternal levels of plasma human immunodeficiency virus type 1 RNA and the risk of perinatal transmission. Women and Infants Transmission Study Group. *N Engl J Med*. Aug 5 1999;341(6):394-402.
9. Briand N, Warszawski J, Mandelbrot L, et al. Is intrapartum intravenous zidovudine for prevention of mother-to-child HIV-1 transmission still useful in the combination antiretroviral therapy era? *Clin Infect Dis*. 2013;57(6):903-914.
10. Paediatrics Protocols For Malaysian Hospitals (3rd edition)
11. Nielsen-Saines K, Watts DH, Veloso VG, et al. Three postpartum antiretroviral regimens to prevent intrapartum HIV infection. *N Engl J Med*. Jun 21 2012;366(25):2368-2379
12. Chi BH, Mudenda V, Levy J et al. Acute and chronic chorioamnionitis and the risk of perinatal human immunodeficiency virus-1 transmission. *Am J Obstet Gynecol* 2006; 194: 174–181.

Adverse Events of ARVs occur with all antiretroviral agents and are a major reason for switching or discontinuation of therapy and poor adherence. Differentiating between antiretroviral-related toxicities and disease complications can be difficult.

Active surveillance for clinical signs and symptoms of adverse events should be initiated during commencement of ART and during subsequent follow-ups to ensure the events are carefully recorded for future reference and managed accordingly.

Principles of Managing Adverse Events

1. Identify the adverse event and assess its possible cause: antiretroviral agents, other medications or other illnesses.
2. Assess severity of toxicities. [See Annex 5 Severity Grading]
3. If the reaction is mild or moderate, do not discontinue ART (except for NVP-induced rash / hepatotoxicity). Implement symptomatic therapy. Counsel and monitor patients, stress the importance of adherence despite toxicity.
4. Moderate or severe toxicities may require substitution of the drug with another of the same ARV class, but with a different toxicity profile. [See Table 6]
5. Severe life-threatening toxicity requires discontinuation of ALL ARV drugs until the patient is stabilized and the toxicity is resolved.
6. If there is intolerance due to an individual drug, a single drug substitution can be made; however, a single drug substitution should not be made if the patient is a known case of virological failure.
7. If there is a need to discontinue ART, all antiretroviral medications must be stopped together. Stopping only one drug can lead to resistance. For stopping regimes with NNRTI, refer to 'Stopping / Interrupting NNRTI'

Table 8.0 • Individual NRTI Drug Substitutions for Toxicity and Intolerance

ARV Drug	Major Toxicities	Risk Factors	Suggested Management
ABC	Hypersensitivity reaction	Presence of HLA-B*5701 gene (test available in select labs only)	Substitute with TDF / ZDV
TDF	• Renal tubular toxicity • Fanconi syndrome • Decrease in bone Mineral density • Hepatic flares	• Underlying kidney disease (avoid if eGFR <50mL/min) • Older age • BMI <18.5 (or bodyweight >50kg) • Underlying diabetes Mellitus & uncontrolled hypertension • Concomitant use of Nephrotoxic drugs or a boosted PI • History of osteomalacia and mineral density fracture • At risk of osteoporosis/ Bone loss • When TDF withdrawn or HBV resistance develops	• Substitute with ZDV / ABC • Use alternative drug for Hep. B (e.g. entecavir)
ZDV	• Anaemia, neutropaenia • Myopathy • Lipodystrophy (rare)	• Baseline anaemia/ neutropaenia • CD4 count ≤ 200 cells/mm^3	• Substitute with TDF / ABC
EFV	• 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 with food.	• Substitute with NVP • If keen to continue in mild depression, closely monitor for deterioration of depression. (care takers adviced to monitor for deterioration of depression)
NVP	• Hepatitis • Severe skin rash (SJS)	• Females with baseline CD4 >250 cells /mm^3 • Males with baseline CD4 >400cells/mm^3	• Substitute with EFV /PI based regime

Table 8.1 • Adverse Events of Antiretroviral Drugs

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

TDF		Diarrhea: • Antimotility agents (e.g., loperamide, diphenoxylate/ atropine) • Monitor pancreatic enzymes Severe GI symptoms: Rehydration and electrolyte replacement as indicated Severe GI symptoms: Rehydration and electrolyte replacement as indicated
Hepatotoxicity		
Associated ARVs	**Comments**	**Management**
All NNRTIs **all PIs** **most NRTIs**	• NNRTI • NVP Usually occurs in the first 2-3 months of treatment. Dose escalation reduces risk of hepatic AE due to hypersensitivity. Higher risk of NVP-associated hepatic AE in ARV-naïve females with baseline CD4 >250 cells/uL and males with baseline CD4 >400 cells/uL. Contraindicated in moderate to severe hepatic impairment (Child-Pugh B or C) NRTI Usually occurs after more than 6 months of therapy – ZDV, d4T (grade 3 / 4: 2–16%) Risk of hepatotoxicity associated with lactic acidosis with microvesicular or macrovesicular hepatic steatosis because of mitochondrial toxicity. Protease inhibitors Usually occurs after weeks to months of treatment Indirect hyperbilirubinemia may occur with IDV (14%) & ATV (35–49%) usage	Symptomatic patients: • Discontinue all ARVs and other potential hepatotoxic agents Asymptomatic patients: • If ALT >5–10x ULN, to consider discontinuing ARVs • After serum transaminases return to normal, start a new ARV regimen without the potential offending agent(s)

Hyperlipidemia		
Associated ARV	**Comments**	**Management**
All PIs (except unboosted ATV); **EFV > NVP**	NNRTIs • EFV is associated with ↑ TG, HDL, LDL (TC ↑ by 20-40%). • Increase in TG, TC and LDL less than with PIs NRTIs • d4T > ZDV > ABC - TG and LDL ↑ PIs • Cause ↑ in LDL, HDL and TG – all RTV-boosted PIs. • TG ↑: LPV/r (3-36%) > DRV/r, ATV/r • Usually seen within 2–3 months of starting PIs.	• Lifestyle modifications (e.g., diet, exercise, smoking cessation) • Consider to switch to agents with less propensity for causing hyperlipidemia Pharmacologic Management: • refer to CPG on Management of Dyslipidemia *Note. Refer to Table 17 & 18: Drug Interactions for interactions between ARV and lipid-lowering agents*
Hypersensitivity Reaction (HSR)		
Associated ARV	**Comments**	**Management**
ABC	• Incidence: Up to 8% • Median onset is 9 days; approximately 90% of reactions occur within the first 6 weeks <u>Symptoms include:</u> • (In descending frequency): fever, skin rash, malaise, nausea, headache, myalgia, chills, diarrhea, vomiting, abdominal pain, dyspnea, arthralgia, and respiratory symptoms. • With continuation of ABC, symptoms may worsen to include hypotension, respiratory distress.	<u>Discontinue ABC and switch to another NRTI</u> • Rule out other causes of symptoms (e.g., intercurrent illnesses such as viral syndromes and other causes of skin rash) • Signs and symptoms usually resolve 48 hours after discontinuation of ABC <u>More severe cases</u>: • Manage with symptomatic support (antipyretic, fluid resuscitation, pressure support if necessary) • Do not rechallenge patients with ABC after suspected HSR, even in patients who are tested (-) for HLA-B*5701.

Lactate : Hyperlactatemia / Lactic Acidosis		
Associated ARV	**Comments**	**Management**
ZDV > other NRTIs	3 clinical syndromes: a) Lactic acidosis with hepatic steatosis b) Symptomatic lactatemia without acidosis / liver failure c) Asymptomatic lactatemia Symptoms include: • Nonspecific GI prodrome (nausea, anorexia, abdominal pain, vomiting), weight loss, and fatigue • Subsequent symptoms : tachycardia, tachypnea, hyperventilation, jaundice, muscular weakness, mental status changes, or respiratory distress • May present with multi-organ failure (e.g., hepatic failure, acute pancreatitis, encephalopathy, and respiratory failure) • Typically present after several months of therapy • Risk & severity increases with time on treatment (usually takes months/ years) but sometimes can occur soon after starting treatment *Note. The half-life of mitochondrial DNA ranges from 4.5 to 8 weeks and hence the time required for clinical recovery after stopping NRTI is 4 to 8 weeks*	Lactate 2-5 mmol/L but asymptomatic: Observe. *Note. Do not measure lactate unless symptomatic* Lactate 2-5mmol/L + symptoms ± Liver abnormality: Stop ARVs Lactate > 5mmol/L or lactic acidosis: • Stop ARVs • Exclude other precipitating factors • Intensive care support • To consider: IV thiamine and/or riboflavin / bicarbonate infusions/ haemodialysis ARV treatment 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		
Associated ARVs	**Comments**	**Management**
ZDV> other NRTIs	• Fat wasting (lipoatrophy): face, arms, leg, buttocks – more likely when NRTIs combined with EFV than with RTV boosted PI • Fat accumulation: Abdomen, neck, gynaecomastia, buffalo hump, multiple lipomas, Cushingoid appearance without Cushing's disease. • Trunk fat ↑ was noted with EFV, PIs and RAL containing regimes, but no causal link has yet been established.	• Switch from thymidine analogs to TDF or ABC, which may slow or halt progression but may not fully reverse effects • Surgical options provide cosmetic improvement: • Lipoatrophy: Facial filling with collagen, synthetic polymers or silicone • Lipodystrophy: Liposuction

Nephrotoxicity / Urolithiasis		
Associated ARV	**Comments**	**Management**
TDF **ATV**	TDF • Symptoms include: ↑ serum creatinine, proteinuria, hypophosphatemia, urinary phosphate wasting, glycosuria, hypokalemia, normal anion gap metabolic acidosis • Concurrent use with PI: ↑ risk ATV • May cause kidney stone / crystal formation	Prevention • Drink at least 1.5 - 2 liters of non Caffeinated fluid per day (preferably water) Treatment • A rise of creatinine clearance >20% from baseline, consider switch to alternative regime (especially those with other coexisting risk factors of renal disease) • Refer to Urologists when indicated
Neuromuscular Weakness Syndrome (ascending)		
Associated Drugs	**Comments**	**Management**
NRTIs	It occurs after months of ARV use. Symptoms: Very rapidly progressive ascending demyelinating polyneuropathy, may mimic Guillain-Barré syndrome	• Discontinue ARVs • Supportive care, including mechanical ventilation if needed • Other measures include plasmapheresis, high-dose corticosteroids, intravenous immunoglobulin, carnitine, acetylcarnitine • Recovery often takes months and ranges from complete recovery to substantial residual deficits; symptoms may be irreversible in some patients *Do not rechallenge patient with offending agent.*
Pancreatitis		
Associated ARVs	**Comments**	**Management**
ddI + TDF	• ddI with d4T or TDF : ↑ frequency • Avoid concomitant use of ddI with d4T or TDF	• Discontinue offending agent(s) • Manage symptoms of pancreatitis (bowel rest, IV hydration, pain control, then gradual resumption of oral intake) • Parenteral nutrition may be necessary in patients with recurrent symptoms upon resumption of oral intake

Rash		
Associated ARV	**Comments**	**Management**
NVP	Rash is greatest in the first 6 weeks of treatment (Malaysian data: >20%). Constitutional symptoms : • Fever> 37 ºC • Blistering • Oral lesions • Conjuctivitis • Significant elevations in LFTs • Facial oedema • Myalgia/arthralgia • Generalized malaise	• In the presence of mild to moderate rash without constitutional symptoms or biochemical hepatitis, the lead-in (200mg od) dose may be continued without dose escalation until rash resolution, but no longer than 28 days total. • However, the drug should be permanently discontinued if constitutional symptoms are present, the rash is severe or hepatitis is present. Also see Stopping / Interrupting NNRTI. If NVP is interrupted for > 7 days, reintroduce with 200mg / day lead-in.
Stevens-Johnson Syndrome (SJS) / Toxic Epidermal Necrosis (TEN)		
Associated ARV	**Comments**	**Management**
NVP>EFV **Others :** **ABC , AZT,** **LPV/r , ATV , DRV**	Incidence : NVP: 0.3%–1% EFV: 0.1% ABC, ZDV, IDV, LPV/r, ATV, DRV: 1–2 case reports	• Discontinue all ARVs and any other possible agent(s) • Do not re-challenge with offending drugs. If offending drug is NVP, may consider use of EFV. • Aggressive symptomatic support

Table 8.2 • ARV Drugs and Common Adverse Events

NRTI	
Drug	**Adverse Events**
ABC	Refer to table 14
3TC	• Minimal toxicity • Severe acute hepatitis flare may occur in HBV co-infected patients who discontinue 3TC.
TDF	• Asthenia, headache, diarrhea, nausea, vomiting, and flatulence • Renal insufficiency , Fanconi syndrome (Renal tubular damage reported, risk of serious renal damage is 0.5%) • Osteomalacia • Potential for decrease in bone mineral density • Severe acute hepatitis flare may occur in HBV co-infected patients who discontinue TDF
ZDV	• Bone marrow suppression: macrocytic anemia or neutropenia • Gastrointestinal intolerance, headache, insomnia, asthenia • Nail pigmentation • Lactic acidosis with hepatic steatosis (rare but potentially life threatening toxicity)

NNRT	
Drug	**Adverse Events**
EFV	• Rash • Central nervous system symptoms • Increased transaminase levels • Painful gynecomastia • False-positive results reported with some cannabinoid and benzodiazepine screening assays
NVP	• Rash, including Stevens-Johnson syndrome • Symptomatic hepatitis, including fatal hepatic necrosis, has been reported
Protease Inhibitor	
Drugs	**Common Adverse Events**
ATZ	• Indirect hyperbilirubinemia • Prolonged PR interval—first degree symptomatic AV block in some pts • Use with caution in pts with underlying conduction defects or on concomitant medications that can cause PR prolongation • Hyperglycemia • Fat maldistribution • Possible increased bleeding episodes in patients with hemophilia • Nephrolithiasis
DRV	• Skin rash (10%)—DRV has a sulfonamide moiety; Stevens-Johnson syndrome and erythrema multiforme have been reported • Hepatotoxicity • Diarrhea, nausea • Headache • Hyperlipidemia • Transaminase elevation • Hyperglycemia • Fat maldistribution • Possible increased bleeding episodes in pts with hemophilia
RTV	• GI intolerance, nausea, vomiting, diarrhea • Paresthesias—circumoral and extremities • Hyperlipidemia (especially hypertriglyceridemia) • Hepatitis • Asthenia • Taste perversion • Hyperglycemia • Fat maldistribution • Possible increased bleeding episodes in pts with hemophilia
Integrase Inhibitors	
DTG	• Insomnia, headache • Hepatotoxicity (higher risk with underlying hepatitis B and C coinfetion and liver disease) • Hypersensitivity reactions (if hypertsensitivity reation, substitute with another class of ART)
RAL	• Increased CK; muscle weakness and rhabdomyolysis • Rash (uncommon)

COMMON ANTIRETROVIRAL THERAPY (ART) DRUG INTERACTIONS

Drug-drug interactions with ART 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 9.0, Table 9.1, Table 9.2 and Table 9.3). An easier option would be to use a HIV drug interaction checker on your smartphone or online. Commonly used by Infectious Diseases physicians is the "HIV iChart" created by the University of Liverpool. This can be downloaded from the App Store or found at www.hiv-druginteractions.org

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

Table 9.1 • Drug Interactions Between NNRTIs and Other Drugs

Concomitant Drug Class	NNRTI	Effect on NNRTI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Anticoagulants / Antiplatelets			
Warfarin	**EFV, NVP**	↑ or ↓ Warfarin possible	Monitor INR and adjust warfarin dose accordingly
Anticonvulsants			
Carbamazepine Phenobarbital Phenytoin	**EFV**	Carbamazepine plus EFV: • Carbamazepine AUC ↓ 27% • EFV AUC ↓ 36% Phenytoin plus EFV: • ↓ EFV • ↓ Phenytoin possible	Monitor anticonvulsant and EFV levels or, if possible, use alternative anticonvulsant to those listed.
	RPV	↓ RPV possible	Contraindicated. Do not coadminister. Consider alternative anticonvulsant.
	NVP	↓ Anticonvulsant and NVP possible	Monitor anticonvulsant and NVP levels and virologic responses or consider alternative anticonvulsant.
Antidepressants			
Bupropion	**EFV**	Bupropion AUC ↓ 55%	Titrate Bupropion dose based on clinical response
Paroxetine	**EFV**	No significant effect	No dosage adjustment necessary
Sertraline	**EFV**	Sertraline AUC ↓ 39%	Titrate Sertraline dose based on clinical response.
Antifungals			
Fluconazole	**EFV**	No significant effect	No dosage adjustment necessary
	NVP	NVP AUC ↑ 110%.	Increased risk of hepatotoxicity possible with this combination. Monitor NVP toxicity or use alternative ARV agent
	RPV	↑ RPV possible No dosage adjustment necessary.	Clinically monitor for breakthrough fungal infection.
Itraconazole	**EFV**	Itraconazole AUC, Cmax, and Cmin ↓ 35% to 44	% Failure to achieve therapeutic itraconazole concentrations has been reported. Avoid this combination if possible. If coadministered, closely monitor itraconazole concentration and adjust dose accordingly.

Concomitant Drug Class	NNRTI	Effect on NNRTI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Antifungals			
Itraconazole	**RPV**	↓ Itraconazole possible ↑ RPV possible	No dosage adjustment necessary. Clinically monitor for breakthrough fungal infection.
	NVP	↓ Itraconazole possible ↑ NVP possible	Avoid combination if possible. If coadministered, monitor itraconazole concentration and adjust dose accordingly.
Posaconazole	**EFV**	Posaconazole AUC ↓ 50%	Avoid concomitant use unless the benefit outweighs the risk. If coadministered, monitor posaconazole concentration and adjust dose accordingly.
	RPV	↓ Posaconazole possible ↑ RPV possible	No dosage adjustment necessary. Clinically monitor for breakthrough fungal infection.
Voriconazole	**EFV**	Voriconazole AUC ↓ 77% EFV AUC ↑ 44%	Contraindicated at standard doses. Dose adjustment: Voriconazole 400 mg BID, EFV 300 mg daily.
	RPV	↓ Voriconazole possible ↑ RPV possible	No dosage adjustment necessary. Clinically monitor for breakthrough fungal infection.
	NVP	↓ Voriconazole possible ↑ NVP possible	Monitor for toxicity and antifungal response and/or Voriconazole level.
Antimalarials			
Artemether/ Lumefantrine		Artemether AUC ↓ 79% Lumefantrine AUC ↓ 56%	Consider alternative ARV or antimalarial drug. If used in combination, monitor closely for antimalarial efficacy and malaria recurrence.
		Artemether AUC ↓ 67% to 72% DHA: • Study results are conflicting. AUC ↓ 37% in one study, no difference in another. Lumefantrine: • Study results are conflicting. Lumefantrine AUC ↓ 25% to 58% in 2 studies but ↑ 56% in another.	Clinical significance unknown. If used, monitor closely for antimalarial efficacy and Lumefantrine toxicity

Concomitant Drug Class	NNRTI	Effect on NNRTI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Antimycobacterials			
Clarithromycin	**EFV**	Clarithromycin AUC↓ 39%	Monitor for effectiveness or consider alternative agent, such as azithromycin, for MAC prophylaxis and treatment.
	NVP	Clarithromycin AUC ↓31%	% Monitor for effectiveness or use alternative agent, such as azithromycin, for MAC prophylaxis and treatment
	RPV	↑ RPV possible	Consider alternative macrolide, such as azithromycin, for MAC prophylaxis and treatment.
Rifabutin	**EFV**	Rifabutin ↓38%	Dose: • Rifabutin150mg/day or • Rifabutin 300 mg 3 times/week if coadministered with a PI.
	NVP	Rifabutin AUC ↑ 17% and metabolite AUC ↑ 24% NVP Cmin ↓ 16%	No dosage adjustment necessary. Use with caution.
	RPV	Rifabutin plus RPV 50 mg once daily compared to RPV 25 mg once daily alone: ←→ RPV AUC, Cmin	Increase RPV dose to 50 mg once daily
Rifampin	**EFV**	EFV AUC ↓ 26%	Maintain EFV dose at 600 mg once daily and monitor for virologic response. Consider therapeutic drug monitoring.
	NVP	NVP ↓ 20% to 58%	Do not coadminister.
	RPV	RPV AUC ↓ 80%	Contraindicated. Do not coadminister.
	DTG	DTG level ↓	Increase DTG to 50mg twice daily

Concomitant Drug Class	NNRTI	Effect on NNRTI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Benzodiazepines			
Alprazolam	**EFV, ETR, NVP, RPV**	No data	Monitor for therapeutic effectiveness of Alprazolam.
Lorazepam	**EFV**	Lorazepam Cmax ↑ 16%, AUC↔	No dosage adjustment necessary.
Midazolam	**EFV**	Significant ↑ Midazolam expected.	Do not coadminister with oral Midazolam. Parenteral Midazolam can be used with caution as a single dose and can be given in a monitored situation for procedural sedation
Cardiac Medications			
Dihydropyridine CCBs	**EFV, NVP**	↓ CCBs possible	Titrate CCB dose based on clinical response.
Diltiazem Verapamil	**EFV**	Diltiazem AUC ↓ 69% ↓ verapamil possible	Titrate Diltiazem or verapamil dose based on clinical response
	NVP	↓ Diltiazem or verapamil possible	
Corticosteroids			
Dexamethasone	**EFV, NVP**	↓ EFV, NVP possible	Consider alternative corticosteroid for long-term use. If Dexamethasone is used with NNRTI, monitor virologic response.
	RPV	Significant ↓ RPV possible	Contraindicated with more than a single dose of Dexamethasone
Hormonal Contraceptives			
	EFV	Ethinyl estradiol ↔ Levonorgestrel (oral) AUC ↓64% Norelgestromin AUC ↓ 64% Etonogestrel (implant) AUC ↓63% Levonorgestrel (implant) AUC ↓ 48%	Use alternative or additional contraceptive methods. Norelgestromin and Levonorgestrel are active metabolites of Norgestimate. Unintended pregnancies were observed in women who used EFV and levonorgestrel implant concomitant
	NVP	Ethinyl estradiol AUC ↓29%, Cmin ↓ 58% Norethindrone AUC ↓ 18% Etonogestrel (metabolite of oral desogestrel) ↓ 22% Levonorgestrel implant: AUC ↑ 30% N	Consider alternative or additional contraceptive methods No dosage adjustment necessary

Concomitant Drug	NNRTI	Effect on NNRTI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Hormonal Contraceptives			
	RPV	Ethinyl estradiol: no significant change Norethindrone: no significant change	No dosage adjustment necessary
HMG-CoA Reductase Inhibitors			
Atorvastatin	**EFV**	Atorvastatin AUC ↓ 32% to 43%	Adjust atorvastatin according to lipid responses, not to exceed the maximum recommended dose.
	RPV	Atorvastatin AUC ←→ Atorvastatin metabolites ↑	No dosage adjustment necessary.
Simvastatin	**EFV**	Simvastatin AUC ↓ 68%	Adjust simvastatin dose according to lipid responses, not to exceed the maximum recommended dose. If EFV is used with a PI/r, simvastatin and lovastatin should be avoided.
	NVP	↓ Lovastatin possible ↓ Simvastatin possible	Adjust lovastatin or simvastatin dose according to lipid responses, not to exceed the maximum recommended dose. If ETR or NVP is used with a PI/r, simvastatin and lovastatin should be avoided.
Pravastatin Rosuvastatin	**EFV**	Pravastatin AUC ↓ 44% Rosuvastatin: no data	Adjust statin dose according to lipid responses, not to exceed the maximum recommended dose.
PDE5 Inhibitors			
Sildenafil	**RPV**	←→ Sildenafil	No dosage adjustment necessary

Table 9.2 • Common PI Drug Interactions and Suggested Management

Concomitant Drug	Protease Inhibitor (PI)	Description of Interaction	Suggested Management
Acid reducer			
Antacids	**ATV/r**	↑pH →↓ATV solubility; ↓ ATV AUC & absorption[3]	Give ATV at least 2 hours before or 1 to 2 hours after antacids or buffered medications.
H2 Receptor Antagonists	**ATV/r**	↑pH ↓ATV solubility; ATV AUC ↓48% when ATV/r was administered 1 hr after a single dose of ranitidine 150mg in a study of 12 healthy volunteers[1]	H2-receptor antagonist can be administered with ATV/r but dose should not exceed a dose equivalent to famotidine 40mg BID in treatment naive patients or 20mg BID in treatment experienced patients.[4] ATV/r should be administered either simultaneously with or at least 10 hrs after H2-receptor antagonist (which leads to only <20% reduction of ATV AUC) [2,3] Note: *PO Famotidine 20mg BID =PO Ranitidine 150mg BID; IV Famotidine 20mg BID = IV Ranitidine 50mg TDS*
Proton Pump Inhibitors (PPIs)	**ATV/r**	AUC of ATV/r ↓ –42-76%.[3,5,6] Mechanism is by reduction of ATV solubility due to increased gastric pH.	Co-administration is not recommended.[3] If co-administration is unavoidable, PPIs should not exceed dose equivalent of omeprazole 20mg OD and should be administered 12hrs apart from ATV/r.
Antifungal			
Fluconazole	**◊ All PIs (except tiprinavir)**	No significant effect[3,7,8,9,10]	No dose adjustment necessary[3,7,8,9,10]
Itraconazole	**ATV/r, DRV/r, LPV/r**	Potential for bidirectional inhibition between itraconazole and PIs[3,7,8,9,10]	Do not exceed itraconazole 200mg /day. Use with caution and monitor for toxicities.[3,7,8,9,10]
Ketoconazole	**ATV/r, DRV/r, LPV/r**	Potential for bidirectional inhibition between ketoconazole and PIs[3,7,8,9,10]	Do not exceed ketoconazole 200mg/day. Use with caution and monitor for toxicities.[3,7,8,9,10]
posaconazole	**ATV/r** **ATV** **DRV/r** **LPV/r**	ATV AUC ↑ 146% ATV AUC ↑ 268% ↑ PI possible ↑ posaconazole possible	Monitor for adverse effects of ATV. If coadministered, consider monitoring posaconazole concentrations. Monitor for PI adverse effects.

Concomitant Drug	Protease Inhibitor (PI)	Description of Interaction	Suggested Management
Antifungal			
Voriconazole	**ATV/r, DRV/r, LPV/r**	Low dose RTV 100mg BD decrease voriconazole AUC by 39%. [10]	Co-administration of voriconazole and ritonavir-boosted PIs should be avoided, unless an assessment of the benefit/risk to the patient justifies the use of voriconazole.[10]
Antibiotics			
Clarithromycin	**ATV (unboosted)**	Clarithromycin AUC ↑ 94%	May cause QTc prolongation. Reduce clarithromycin dose by 50%. Consider alternative therapy (eg, azithromycin).
	All PI/r,	↑ Clarithromycin expected DRV/r ↑ Clarithromycin AUC 57% FPV/r ↑ Clarithromycin possible LPV/r ↑ Clarithromycin expected RTV 500 mg BID↑ Clarithromycin 77% SQV unboosted ↑ Clarithromycin 45% TPV/r ↑ Clarithromycin 19% Clarithromycin ↑ unboosted SQV 177% Clarithromycin ↑TPV 66%	Consider alternative macrolide (eg, azithromycin) Monitor for clarithromycin-related toxicities or consider alternative macrolide (eg, azithromycin). Reduce clarithromycin dose by 50% in patients with CrCl 30–60 mL/min. Reduce clarithromycin dose by 75% in patients with CrCl <30 mL/min.
Erythromycin	**DRV/r, LPV/r,**	Erythromycin concentrations may increase but no data on the extent of interaction. [7,8,9,1]	Careful monitoring of therapeutic and adverse effects is recommended. [7,8,9,10]
Rifampicin	**All PIs**	Significant decrease in PI Concentrations (up to >80%)[7,8,9,10]	Do not co administer rifampicin and PIs.[7,8,9,10]
Rifabutin		Compared to rifabutin (300mg daily) alone	Rifabutin 150mg once daily or 300mg 3 times a week.
Antimalarials			
Artemether/ Lumefantrine	**DRV/r**	Artemether AUC ↓ 16% DHA[a] AUC ↓ 18% Lumefantrine AUC ↑ 2.5-fold	Clinical significance unknown. If used, monitor closely for antimalarial efficacy and lumefantrine toxicity.
	LPV/r	Artemether AUC ↓ 40% DHA AUC ↓ 17% Lumefantrine AUC ↑ 470%	
Artesunate/ Mefloquine	**LPV/r**	dihydroartemisinin AUC ↓ 49% mefloquine AUC ↓ 28% LPV ←→	Clinical significance unknown. If used, monitor closely for antimalarial efficacy

Concomitant Drug	Protease Inhibitor (PI)	Description of Interaction	Suggested Management
Antimalarials			
Atovaquone/ Proguanil	ATV/r LPV/r	ATV/r ↓ atovaquone AUC 46% and ↓ proguanil AUC 41% LPV/r ↓ atovaquone AUC 74% and ↓ proguanil AUC 38%	No dosage recommendation. Consider alternative drug for malaria prophylaxis, if possible
Mefloquine	RTV	With RTV 200 mg BID: RTV AUC ↓ 31%, Cmin↓ 43%; nn mefloquine	Use with caution. Effect on exposure of RTV-boosted PIs is unknown.
Anticonvulsants			
Carbamazepine (CBZ)	ATV/r, LPV/r	Co-administration may increase CBZ levels (up to 46%) and decrease PI concentrations.[3,8,9,14]	Consider alternative anticonvulsant or monitor levels of both drugs and assess virological response. [3,8,9]
	DRV/r	CBZ AUC ↑45%. No significant effect on DRV exposure.[7]	Monitor anticonvulsant level and adjust dose accordingly. [7]
Lamotrigine (LTG)	LPV/r	LTG AUC ↓ 50% due to induction of Glucoronidation metabolism.[15] No effect on LPV/r.	Titrate lamotrigine dose to effect. A similar interaction is possible with other RTV boosted PI.[3,8,10,1]
Phenytoin (PHT) / Phenobarbitone (PHB)	ATV/r, DRV/r, LPV/r	Both PI concentrations and PHT/PHB levels may decrease due to bi-directional interactions. [3,7,8,9,10]	Consider alternative anticonvulsant or monitor levels of both drugs and assess virologic response. Do not co-administer with LPV/r once daily. [3,7,8,9,10]
Valproic Acid (VPA)	ATV/r, DRV/r, LPV/r	Possible decrease in VPA level by ritonavir (induces glucoronidation) but no significant effect on PIs.[3,7,8,10,16]	Monitor anticonvulsant level and adjust dose accordingly. [3,7,8,10,16]
Benzodiazepines			
Alprazolam Clonazepam Diazepam	All PIs	↑ benzodiazepine possible RTV (200 mg BID for 2 days) ↑ alprazolam half-life 222% and AUC 248%	Consider alternative benzodiazepines such as lorazepam, oxazepam, or temazepam.
Lorazepam	All PIs	No data	These benzodiazepines are metabolized via non-CYP450 pathways; thus, there is less interaction potential than with other benzodiazepines

Concomitant Drug	Protease Inhibitor (PI)	Description of Interaction	Suggested Management
Benzodiazepines			
Midazolam	**All PIs**	↑ Midazolam expected	Do not coadminister oral midazolam and PIs. Parenteral midazolam can be used with caution when given as a single dose in a monitored situation for procedural sedation Monitor clinical effect and withdrawal symptoms.
Zolpidem	**Δ All PIs**	Potential CYP3A4 enzyme inhibition by PIs and increase in Zolpidem concentrations.[17]	Consider starting zolpidem at lower dosage or use alternative benzodiazepine.
Hormonal Contraceptives			
Hormonal Contraceptives	**Δ ATV/r**	Ethinyl estradiol AUC ↓19% [19]	Oral contraceptive should obtain at least 35mcg of ethinylestradiol.[19]
	Δ DRV/r, Δ LPV/r	Ethinyl estradiol AUC ↓ 44-55% [20,21] No clinically significant interactions.[8,9]	Use alternative or additional method [7,9]
HMG-CoA Reductase Inhibitors			
Atorvastatin	**ATV, ATV/r DRV/r**	↑ Atorvastatin possible	Titrate atorvastatin dose carefully and use lowest dose necessary.
Pravastatin	**ATV/r**	No data	Use lowest starting dose of pravastatin and monitor for efficacy and adverse effects.
	DRV/r	With DRV/r, pravastatin AUC • ↑ 81% following single dose of pravastatin • ↑ 23% at steady state	Use lowest possible starting dose of pravastatin with careful monitoring
	LPV/r	Pravastatin AUC ↑ 33%	No dose adjustment necessary
Rosuvastatin	**ATV/r, LPV/r**	ATV/r ↑ Rosuvastatin AUC 3-fold and Cmax ↑7-fold LPV/r ↑ Rosuvastatin AUC 108% and Cmax ↑ 366%	Titrate rosuvastatin dose carefully and use the lowest necessary dose. Do not exceed 10 mg rosuvastatin daily.
	DRV/r	Rosuvastatin AUC ↑ 48% and Cmax ↑ 139%	Titrate rosuvastatin dose carefully and use the lowest necessary dose while monitoring for toxicities
Simvastatin	**All PIs**	Significant ↑ Simvastatin level	Contraindicated. Do not coadminister.

Concomitant Drug	Protease Inhibitor (PI)	Description of Interaction	Suggested Management
Cortocosteroids			
Budesonide Fluticasone, Mometasone Systemic/ Inhaled	**All PIs**	↓ PI levels possible ↑ glucocorticoids	Coadministration can result in adrenal insufficiency and Cushing's syndrome. Do not coadminister unless potential benefits of systemic budesonide outweigh the risks of systemic corticosteroid adverse effects
Dexamethasone Systemic	**All PIs**	↓ PI levels possible	Use systemic dexamethasone with caution. Consider alternative corticosteroid for long-term use.
Prednisone	**All PIs**	↑ Prednisolone poss	Use with caution. Coadministration can result in adrenal insufficiency and Cushing's syndrome. Do not coadminister unless potential benefits of prednisone outweigh the risks of systemic corticosteroid adverse effects.
Cardiac Medications			
Antiarrhythmics	**All PIs**	↑ Antiarrhythmic possible	Use with caution.
Amiodarone	**All PIs**	↑ both Amiodarone and PI possible	Use with caution. Monitor for amiodarone toxicity and consider ECG and amiodarone drug level monitoring.
Beta-blockers	**All PIs**	↑ Beta-blockers possible	May need to decrease beta-blocker dose; adjust dose based on clinical response. Consider using beta-blockers that are not metabolized by CYP450 enzymes (eg, atenolol, labetalol, nadolol, sotalol)
Calcium Channel Blockers (CCBs) (except diltiazem)	**All PIs**	↑ dihydropyridine possible ↑ verapamil possible	Use with caution. Titrate CCB dose and monitor closely.
Digoxin	**All PIs**	RTV (200 mg BID) ↑ Digoxin AUC 29% and ↑ half-life 43%	Use with caution. Monitor digoxin levels. Digoxin dose may need to be decreased. Titrate initial digoxin dose.
Diltiazem	**ATV/r, ATV** **DRV/r, LPV/r**	Unboosted ATV ↑ Diltiazem AUC 125% Greater ↑ likely with ATV/c or ATV/r ↑ Diltiazem possible	Decrease diltiazem dose by 50%. ECG monitoring is recommended. Use with caution. Adjust diltiazem according to clinical response and toxicities.

Concomitant Drug	Protease Inhibitor (PI)	Description of Interaction	Suggested Management
Antidepressants, Anxiolytics and Antipsychotics			
Fluvoxamine	All PIs	↑ or ↓ PI possible	Consider alternative therapeutic agent.
Other Selective Serotonin Reuptake Inhibitors (SSRIs) (eg, citalopram, escitalopram, fluoxetine, paroxetine, sertraline)	RTV DRV/r ATZ/r,LPV/r	Esitalopram ↔ paroxetine AUC ↓ 39% sertraline AUC ↓ 49% No data	Titrate SSRI dose based on clinical response
Quetiapine	All PIs	↑ Quetiapine expected	Starting quetiapine in a patient receiving a PI: • Start quetiapine at the lowest dose and titrate up as needed. Monitor for quetiapine effectiveness and adverse effects. Starting a PI in a patient receiving a stable dose of quetiapine: • Reduce quetiapine dose to 1/6 of the original dose. Closely monitor for quetiapine effectiveness and adverse effects.
Other Antipsychotics (eg,perphenazine, risperidone)	All PIs	↑ Antipsychotic possible	Titrate antipsychotic dose using the lowest initial dose, or adjust maintenance dose accordingly. Monitor for toxicities.
Tricyclic Antidepressants Amitriptyline, Desipramine, Doxepin, Imipramine, Nortriptyline	All PIs	↑ TCA expected	Use lowest possible TCA dose and titrate based on clinical assessment and/or drug levels.
Anticoagulants and Antiplatelets			
Apixaban	All PIs	↑ Apixaban expected	Avoid concomitant use
Dabigatran	All PIs	↑ Dabigatran possible	
Rivaroxaban	All PIs	↑ Rivaroxaban	
Ticagrelor	All PIs	↑ Ticagrelor expected	
Warfarin	All PIs	↓ Warfarin possible	Monitor INR closely when stopping or starting PI/r and adjust warfarin dose accordingly.

Concomitant Drug	Protease Inhibitor (PI)	Description of Interaction	Suggested Management
Immunosuppressants			
Cyclosporine, Everolimus, 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 with specialist as necessary.
Miscellaneous Drugs			
Salmeterol	**All PIs**	↑ Salmeterol possible	Do not coadminister because of potential increased risk of salmeterol-associated cardiovascular events.
Colchicine	**All PIs**	significant ↑ colchicine expected	For Treatment of Gout Flares: • Colchicine 0.6 mg x 1 dose, followed by 0.3 mg 1 hour later. Do not repeat dose for at least 3 days. For Prophylaxis of Gout Flares: • Colchicine 0.3 mg once daily or every other day For Treatment of Familial Mediterranean Fever: • Do not exceed colchicine 0.6 mg once daily or 0.3 mg BID. Do not coadminister in patients with hepatic or renal impairment
Metformin	**DTG**	DTG ↑ metformin levels approximately 2-fold	close monitoring for metformin adverse effects is advisable

Table 9.3 • Common Integrase Inhibitors Interactions and Suggested Management

Concomitant Drug Class	Integrase inhibitor	Effect on NNRTI and/ or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Aluminium, Magnesium ± Calcium-Containing Antacids	**RAL**	Al-Mg Hydroxide Antacid: • RAL Cmin ↓ 54% to 63% $CaCO_3$ Antacid: • RAL Cmin ↓ 32%	Do not coadminister RAL and AlMg hydroxide antacids. Use alternative acid reducing agent. No dosing separation necessary when coadministering RAL and $CaCO_3$ antacids
	DTG	Absorption of DTG may be reduced when the ARV is coadministered with polyvalent cations	DTG should be taken at least 2 hours before or 6 hours after cation-containing antacids or laxatives.
PPIs	**RAL**	RAL AUC ↑ 212% and Cmin ↑46%	No dosage adjustment necessary

Concomitant Drug Class	Integrase inhibitor	Effect on NNRTI and/ or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Antidepressants, Anxiolytics and Antipsychotics			
SSRIs **Citalopram** **Escitalopram** **Fluoxetine** **Paroxetine** **Sertraline**	**RAL**	←→ RAL ←→ citalopram	No dosage adjustment necessary
Antidepressants, Anxiolytics and Antimycobacterials			
Rifabutin **Rifampicin**	**RAL**	AL AUC ↑ 19% and Cmin ↓ 20%	No dosage adjustment necessary
	RAL	RAL 400 mg: • RAL AUC ↓40%, Cmin ↓ 61% Compared with RAL 400 mg BID alone, Rifampin with RAL 800 mg BID: • RAL AUC ↑ 27%, Cmin ↓ 53%	Dose: • RAL 800 mg BID Monitor closely for virologic response or consider using rifabutin as an alternative rifamycin
	DTG		Increase DTG to 50mg BID
Hormonal Contraceptives	**RAL**	No clinically significant effect	No dosage adjustment necessary
Polyvalent Cation Supplements Mg, Al, Fe, Ca, Zn, including multivitamins with minerals	**All INSTIs**	↓ INSTI possible DTG n when administered with Ca or Fe supplement simultaneously with food	If coadministration is necessary, give INSTI 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. DTG and supplements containing Ca or Fe can be taken simultaneously with food. Many oral multivitamins also contain varying amounts of polyvalent cations; the extent and significance of chelation is unknown.

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

REFERENCES

1. Klein CE, Chiu YL, Cai Y, et al. Effects of acid-reducing agents on the pharmacokinetics of lopinavir/ritonavir and ritonavir-boosted atazanavir. J Clin Pharmacol. 2008; 48(5):553-62.
2. Wang X, Boffito M, Zhang J, et al. Effects of the H2-receptor antagonist famotidine on the pharmacokinetics of atazanavir-ritonavir with or without tenofovir in HIV-infected patients. AIDS Patient Care STDS 2011; 25(9):509-15.
3. Reyataz Summary of Product Characteristics, Bristol-Myers Squibb Pharmaceuticals Ltd, April 2012.
4. Agarwala S, Thal G, Nettles R, Bertz R. Further information on the administration of H2-receptor antagonists with atazanavir. J Acquir Immune Defic Syndr, 2006, 42: 516.
5. Zhu L, Persson A, Mahnke L, et al. Effect of low-dose omeprazole (20mg daily) on the pharmacokinetics of multiple-dose atazanavir with ritonavir in healthy subjects. J Clin Pharmacol, 51.3 (2011): 368-377
6. Tomilo DL, Smith PF, Ogundele AB, et al. Inhibition of atazanavir oral absorption by lansoprazole gastric acid suppression in healthy volunteers. Pharmacotherapy, 2006; 26:341-6.
7. Prezista Summary of Product Characteristics, Janssen-Cilag Ltd, June 2012.
8. Crixivan Summary of Product Characteristics, Merck Sharp & Dohme Ltd, February 2012.
9. Kaletra Prescribing Information, Abbott Laboratories, May 2012.
10. Norvir Prescribing Information, Abbott Laboratories, February 2012.
11. Mummaneni V, Randall D, Chabuel D, et al. Steady state pharmacokinetic interaction study of atazanavir with clarithromycin in healthy subjects. 42nd ICAAC, San Diego, September 2002, abstract H-1717.
12. Sekar VJ, Spinosa-Guzman S, De Paepe E, et al. DArunavir/Ritonavir Pharmacokinetics Following Coadministration with Clarithromycin in Healthy Volunteers. J Clin Pharmacol 2008; 48(1):60-5.
13. Boruchoff SE, Sturgill MG, Grasing KW. The steady-state disposition of indinavir is not altered by the concomitant administration of clarithromycin. Clin Pharmacol Ther, 2000; 67:351–9.
14. Bates DE, Herman RJ. Carbamezepine toxicity induced by lopinavir/ritonavir and nelfinavir. Ann Pharmacother, 2006; 40: 1190-1195.
15. Van der Lee, M et al. The effect of lopinavir/ritonavir on the pharmacokinetics of lamotrigine in healthy subjects. 6th International Workshop on Clinical Pharmacology of HIV Therapy, Quebec, April 2005, abstract 12.
16. Peterson D, Cruttenden, et al. Effects of valproic acid coadministration on plasma efavirenz and lopinavir concentrations in human immuno deficiency virusinfected adults. DiCenzo R, Antimicrob Agents Chemother, 2004, 48: 4328-4331.
17. Greenblatt DJ, von Moltke LL, Harmatz JS, et al. Alprazolam-Ritonavir Interaction: Implications for Product Labeling. Clin Pharmacol Ther 2000; 67(4):3541. Lexi-Comp, Inc. (Lexi-DrugsTM). Lexi-Comp, Inc.; January 29, 2011.
18. Zhang J, Chung E, Yones C, et al. The Effect of Atazanavir/Ritonavir on the Pharmacokinetics of An Oral Contraceptive Containing Ethinyl Estradiol and Norgestimate in Healthy Women. Antivir Ther, 2011: 16(2):157-64.
19. Vogler MA, Patterson K, Kamemoto L, et al. Contraceptive Efficacy of Oral and Transdermal Hormones When Co-administered with Protease Inhibitors in HIV-1 Infected Women: Pharmacokinetic Results of ACTG Trial A5188. J Acquir Immune Defic Syndr., 2010; 55(4):473-83.
20. Xarelto Summary of Product Characteristics, Bayer Plc, May 2012.
21. Sekar VJ, Lefebvre E, Guzman SS, et al. Pharmacokinetic Interaction Between Ethinyl Estradiol, Norethindrone and Darunavir With Low-Dose Ritonavir in Healthy Women. Antivir Ther, 2008; 13(4):563-9.
22. Sekar VJ, et al. Pharmacokinetic drug-drug interaction between the new HIV protease inhibitor darunavir (TMC114) and the lipid-lowering agent pravastatin. 8th International Workshop on Clinical Pharmacology of HIV Therapy, Budapest, April 2007, abstract 54.
23. Stanley, Sharilyn K. Guidelines for the use of antiretroviral agents in HIV-infected adults and adolescents. Morbidity and Mortality Weekly Report: Recommendations and Reports (1998): 39-82.

CHARPTER 10

TUBERCULOSIS AND HIV CO-INFECTION

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

10.1 Isoniazid Prophylaxis Therapy (IPT)

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

10.2 ART in HIV Individuals with TB

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

However earlier ART is not associated with reduction in deaths in patients with CD4 >50cells/mm^3 if there is no evidence of serious HIV disease.[3,4] Deferral of ART initiation until the maintenance phase of TB treatment may be warranted in the setting of HIV and CNS-TB co-infection, as early ART treatment is associated with higher mortality.[5]

10.3 Optimal Timing of ART in Treatment-Naive Patients

1. Initiation of ART is warranted regardless of CD4 count in TB-HIV co-infected patients
2. Optimal timing of integrated HIV and TB therapy depends on the patient's immune status:
   a. In patients with Pulmonary TB (smear positive):
      - CD4 < 50 cells/mm^3 – early ART (within 2 weeks of initiation of TB therapy)
      - CD4 50 - 250 cells/mm^3 – timing of ART depends on severity of HIV (In the presence of low Karnofsky score, low body mass index, low haemoglobin, low albumin, organ system dysfunction or extent of disease, ART should be initiated within 2–4 weeks of TB therapy. Otherwise, start within 8–12 weeks of TB therapy)
      - CD4 > 250 cells/mm^3 – ART can be started during maintenance phase of TB therapy
3. Other clinical considerations of starting ART includes tolerability to TB therapy, ability to swallow multiple pills, risk of IRIS, and drug toxicity
4. For TB meningitis, initiation of ART is deferred to maintenance phase (after 2 months of intensive phase) as early ART initiation is associated with higher adverse events[5]

10.4 Immune Reconstitution Inflammatory Syndrome (IRIS)

The risk of IRIS depends on baseline CD4 cell count and the timing of ART in relation to TB therapy. The paradoxical reaction that follows the commencement of anti-TB for pulmonary TB is usually characterized by fever, malaise, weight loss, and worsening respiratory symptoms. Transient worsening of radiographic abnormalities, including new parenchymal opacities and progressive intrathoracic lymph node enlargement may also occur.[6] The risk of IRIS is increased in patients with initial CD4 count <100 cells/mm^3 and in patients with large reduction in viral load and a larger increase in CD4 count.[7-8]

10.5 Choice of ART in Combination with Rifampicin Based Anti-TB Regime

Combination of backbone (2 NRTIs) and base (either a non-nucleoside reverse transcriptase inhibitor, protease inhibitor or integrase strand transfer inhibitor) is recommended.

10.5.1 Nucleoside/Nucleotide Reverse Transcriptase Inhibitors (NRTI)

- There is no significant interaction between NRTI with rifampicin.

10.5.2 Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTI)

- Rifampicin is associated with reduction in concentration of NNRTI. However, reduction of nevirapine concentration with concomitant rifampicin is greater thanwith efavirenz. For patients on rifampicin-based anti-TB regime, initiation of efavirenz-based therapy is recommended. The standard dosage of efavirenz of 600mg daily is recommended.[9]

- Virologically suppressed patient on nevirapine-based therapy who developed TB can continue with the same ART regime. If nevirapine is initiated with rifampicin, it is recommended to start nevirapine 200mg bd from the start. (Initiation of the two week lead-in phase of once-daily dosing dose of nevirapine is not recommended as it can increase risk of virological failure)

10.5.3 Protease Inhibitors (PI)

- Use of rifabutin instead of rifampicin is recommend the ART regime containsa protease inhibitor. The recommended dosage of rifabutin is reduced to 150mg daily or 300mg 3 times-weekly. This applies for both with or without ritonavir boosted PI.

10.5.4 Integrase Inhibitors

- Raltegravir should be used with caution together with rifampicin as the latter may reduce raltegravir drug concentration by 40-60%. For use with rifampicin, the recommended dosing of raltegravir is 800mg bd.[10]
- Standard dosing of raltegravir (400mg bd) is recommended for use with rifabutin.
- Rifabutin does not affect dolutegravir concentration.

ALL other ARTs do not have significant drug interaction with other first-line and second-line anti-TB drugs.

10.6 Introduction of TB Therapy in HIV Patients Already on ART

TB therapy should be started as soon as possible in patients who are already on ART. If patients have already achieved viral load suppression and tolerate ART well, it is preferable to initiate rifampicin-based anti-TB that will not lead to significant interaction that could interfere with viral suppression.

- In patient on ART containing NNRTI, rifampicin-based anti-TB is preferred
- In patient on ART containing PI or integrase inhibitor, rifabutin-based anti-TB is preferred

The duration of rifampicin-containing TB treatment in HIV patients should be at least 6 months.

10.7 Multi-Drug Resistant TB and HIV

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

10.8 Pneumocystis Jiroveci Prophylaxis

Prophylaxis against Pneumocystis jiroveci should be given to all HIV-infected patients with active TB disease regardless of CD4 cell count.

REFERENCES

1. Akolo C, Adetifa I, Shepperd S, Volmink J. Treatment of latent tuberculosis infection in HIV infected persons. *Cochrane database Sys Rev.* 2010. 20;(1):CD000171.
2. Getahun H, Kittikraisak, Heilig CM, et al. Development of a standardized screening rule for tuberculosis in people living with HIV in resource-constrained settings: Individual participant data meta-analysis of observational studies. *PLoS Medicine.* 2011; 8(1):1-14.
3. Piggott DA, Karakousis PC. Timing of Antiretroviral Therapy for HIV in the Setting of TB Treatment. *Clin Dev Immunol.* 2011.2011:103917.
4. AbdoolKarim SS, Naidoo K, Grobler A, et al. Integration of antiretroviral therapy with tuberculosis treatment. *N Engl J Med.* 2011; 365(16):1492-1501.
5. Torok ME, Yen NT, Chau TT, et al. Timing of initiation of antiretroviral therapy in human immunodeficiency virus (HIV)–associated tuberculous meningitis. *Clin Infect Dis.* 2011;52(11):1374 1383.
6. Manabe YC, Breen R, Perti T, Girardi E, Sterling TR. Unmasked tuberculosis and tuberculosis immune reconstitution inflammatory disease: a disease spectrum after initiation of antiretroviral therapy. *J Infect Dis.* 2009;199(3):437-444.
7. Dheda L, Lampe FC, Johnson MA, Lipman MC. Outcome of HIV-associated tuberculosis in the era of highly active antiretroviral therapy. *J Infect Dis.* 2004;190(9):1670-1676.
8. Navas E, Martín-Dávila P, Moreno L, et al. Paradoxical reactions of tuberculosis in patients with the acquired immunodeficiency syndrome who are treated with highly active antiretroviral therapy. *Arch Intern Med.* 2002;162(1):97-99.
9. Boulle A, Van Cutsem G, Cohen K, et al. Outcomes of nevirapine- and efavirenz-based antiretroviral therapy when coadministered with rifampicin-based antitubercular therapy. *JAMA.* 2008;300(5):530 539.
10. Grinsztejn B, De Castro N, Arnold V, et al. Raltegravir for the treatment of patients co-infected with HIV and tuberculosis (ANRS 12 180 Reflate TB): a multicentre, phase 2, non-comparative, open-label, randomized trial. *Lancet Infect Dis.* 2014;14:459-467.

Hepatitis B virus (HBV) and HIV coinfection is common and factors affecting the prevalence of chronic HBV include age at time of infection and mode of acquisition. The progression of chronic HBV to cirrhosis, end-stage liver disease, or hepatocellular carcinoma is more rapid in HBV/HIV coinfected persons compared to persons with HBV alone.

11.1 Effects of HIV on HBV Disease Progression

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

11.2 Effects of ARVs on HBV

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

Goals of Therapy

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

Pre-Treatment Assessments:

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

11.3 Treatment Recommendations for HBV and HIV Co-infection

- Advised to abstain from alcohol and receive hepatitis A vaccination if the patient is not immunized.
- Important to monitor HBV DNA levels in HBV/HIV Co-infected person because the elevations of transaminase levels do not correlate with the level of HBV replications.
- As it is now recommended to start ART irrespective of CD4 cell count or WHO clinical stage, all HIV/HBV Co-infected individuals will be treated as long as the ART regime includes two active drugs with anti-HBV action.

- The suggested ARVs regime should consist of a combination of Tenofovir and Lamivudine or Emtricitabine as the NRTI backbone[2]
- The duration of treatment for treatment of HBV / HIV co-infection is lifelong[3].

In setting where HIV/HBV co-infected individuals not keen to initiate ART regardless of CD4

- HBV status will become the determining factor to guide physician to initiate therapy
- Decision to treat HBV infection depends on ALT, HbeAg status, HBV DNA levels and whether patient has any evidence of liver cirrhosis. (Refer figure 1 and 2)
- Patient whose ALT <1.5-2 ULN, HBeAg negative and HBV DNA $<10^4$ copies/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.
- Recent guideline recommends that HBsAg-positive adults with decompensated cirrhosis be treated with antiviral therapy indefinitely regardless of HBV DNA level, HBeAg status, or ALT level to decrease risk of worsening liver-related complications.[3]

Figure 11.1 • HBV Treatment if HbeAg+

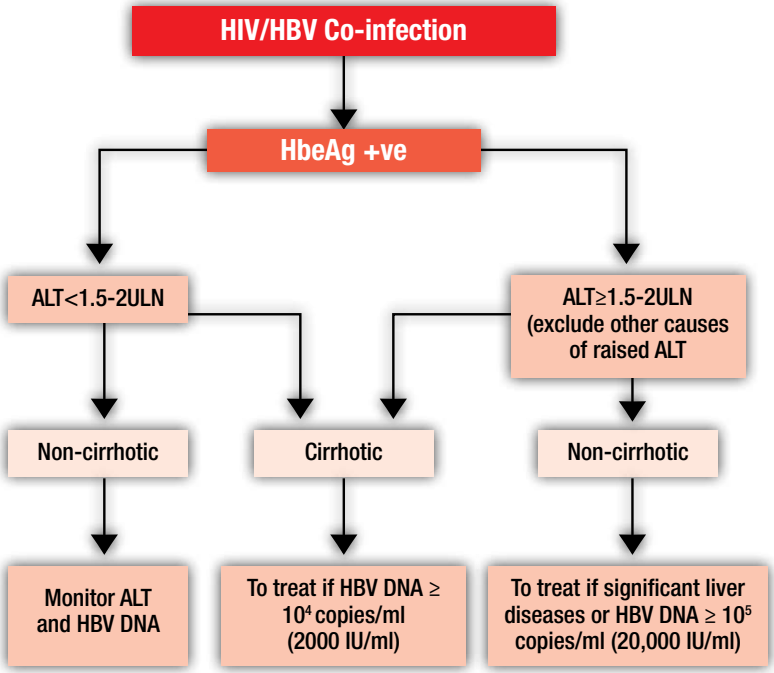
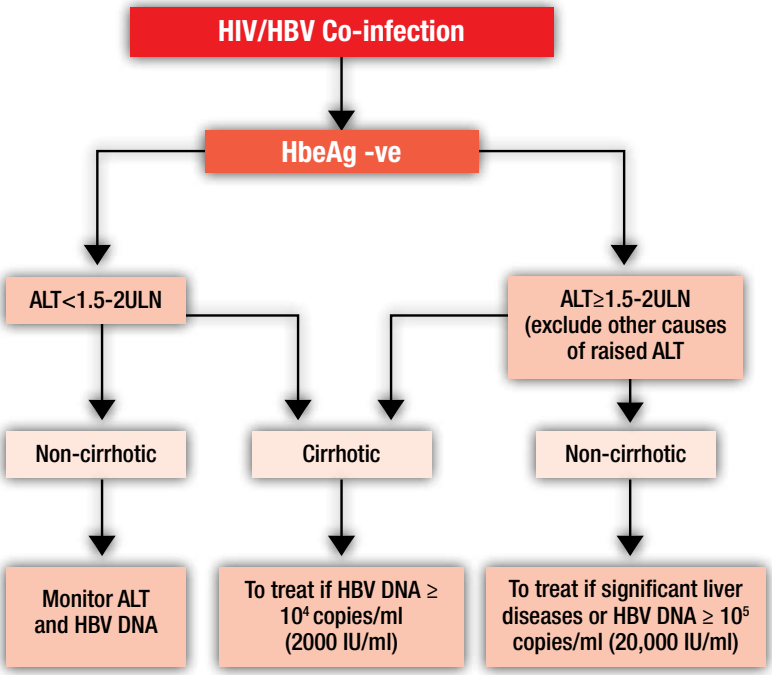


Figure 11.2 • HBV Treatment if HbeAg-



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

REFERENCES

1. Thio CL, Seaberg EC, Skolasky R, Jr., et al. HIV-1, hepatitis B virus, and risk of liver-related mortality in the Multicenter Cohort Study (MACS). *Lancet.* Dec 14 2002; 360(9349):1921-1926.
2. Matthews G.V., Avihinsanon A, Lewin SR, et al., A randomized trial of combination hepatitis B therapy in HIV/HBV coinfected antiretroviral naïve individuals in Thailand. *Hepatology* 2008;48(4): 1062-1069.
3. Norah A. Terrault, Natalie H. Bzowej, Kyong-Mi Chang, Jessica P. Hwang, Maureen M. Jonas, and M. Hassan Murad. AASLD Guidelines for Treatment of Chronic Hepatitis B. Hepatology. Jan 2016.

CHAPTER 12

HIV AND HEPATITIS C CO-INFECTION

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

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

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

12.1 Effects of HCV/HIV Co-Infection

Co-infected patients are less likely to clear HCV viraemia following acute HCV infection and have higher HCV RNA viral loads. They also have more rapid progression of liver fibrosis which leads to a higher rate of end-stage liver disease and mortality[6].

12.2 Effects of Antiretrovirals on HCV Infection

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

12.3 Goal of Treatment

Cure: Sustained Virological Response (SVR)

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

12.4 Candidates Considered for HCV Treatment

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

Consider treatment in these patients:

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

When considering Peg IFN and/or RBV therapy:

1. Patients with psychiatric, ophthalmologic, respiratory, cardiac or neurological illnesses should be on regular treatment and follow up from the respective specialities.
2. Has negative TB workout (CXR, ± Mantoux, ± sputum)

12.5 Pre-treatment Assessment

12.5.1 Diagnosis

1. Anti-HCV antibody
2. If CD4 <100 and HCV antibody is negative but HCV infection is suspected, HCV RNA is recommended
3. HCV RNA viral load
4. HCV genotype

12.5.2 Status of Liver Damage

1. Stage the fibrosis (Fibro Scan, liver biopsy)
2. Hepatic synthetic function (Liver function test, coagulation profile, albumin)
3. Ultrasound of the hepatobiliary system and alpha-feto protein (if suspect liver cirrhosis or hepatocellular carcinoma (HCC))

12.5.3 Others

1. Full blood count, renal profile, ECG
2. CD4 count and HIV RNA viral load
3. Additional test when using Peg IFN ± RBV:
   a. Thyroid function test
   b. UPT (female patients)

12.6 Treatment Recommendation for HCV/HIV Co-infection[10]

12.6.1 General

1. Abstain from alcohol
2. Hepatitis A and B vaccination if not immune
3. Those receiving ART and treatment for HCV require close monitoring because of potential drug-drug interactions (DDI) and increased risk for drug toxicity

12.6.2 Antiviral Agents

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

12.6.3 Treatment Options[12, 13]

a) Combination of Peg-IFN plus weight-based ribavarin

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

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

b) Preferred ART Regime

Initiating ART should follow the same principles as in HIV mono-infection

- Tenofovir + Lamivudine/Emtricitabine + Efavirenz OR
- Abacavir + Lamivudine + Efavirenz

Avoid: Zidovudine: risk of anaemia

c) Direct Acting Antiviral (DAA) ± RBV [14-22]

DAAs registered in Malaysia include simeprevir, sofosbuvir, daclatasvir, sofosbuvir/ledipasvir, 3D (Ombistasvir/paritaprevir/ritonavir/ dasabuvir).

Duration of treatment ranges from 12-24 weeks depending on presence of liver cirrhosis, genotype and previous hepatitis C treatment experience.

A shorter duration of 8 weeks treatment with of Sofosbuvir/Ledipasvir may be considered for genotype 1, treatment naïve non-cirrhotic patients with HCV RNA <6 million copies/ml.

12.6.4 Drug-Drug Interactions (DDIs) to Consider When Using DAAs

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

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

REFERENCES

1. Mathers BM et al. Global epidemiology of injecting drug use and HIV among people who inject drugs: a systematic review. *Lancet*, 2008, 372: 1733-1745.
2. Easterbrook P, Sands A, Harmanci H. Challenges and priorities in the management if HIV/HBV and HIV/HCV coinfection in resource-limited settings. Seminars in Liver Disease, 2012, 32:147-157.
3. Takako U, Maria IL. Viral hepatitis and human immunodeficiency virus co-infections in Asia. *World J Virol*. 2015; 4(2): 96–104.
4. Koziel MJ, Peters MG. Viral hepatitis in HIV infection. *NEJM*, 2007, 356:1445-1454.
5. Sulkowski MS. Viral hepatitis and HIV coinfection. *J Hepatology,* 2008, 48:353-367.
6. Asselah T, Marcellin P. New direct-acting antivirals' combination for the treatment of chronic hepatitis C. *Liver Int* 2011; 31(suppl 1):68–77.
7. Brau N, Salvatore M, Rios-Bedoya CF et al. Slower fibrosis progression in HIV/HCV co infected patients with successful HIV suppression using antiretroviral therapy. *J Hepatology*, 2006, 44(1): 47-55.
8. Sulkowski MS, Mast EE, Seef LB, Thomas DL. Hepatitis C virus infection as an opportunistic disease in persons infected with *HIV. Clin Infect Dis*, 2000, 30 Suppl1: S77-84.
9. Berenguer J et al. Sustained virological response to IFN plus ribavar in reduces liver-related complications and mortality in patients with HIV and HCV. *Hepatology* 2009, 50:407-413.
10. World Health Organisation (WHO) guidelines for the screening, care and treatment of persons with chronic hepatitis C infection. Updated version April 2016.
11. Swathilyengar, KiuTay-Teo, Sabine Vogler, Peter Beyer, Stefan Wiktor, Kees de Joncheere, Suzanne Hill. Prices, Costs, and Affordability of New Medicines for Hepatitis C in 30 Countries: An Economic Analysis. *PLOS Medicine* doi:10.1371/journal.pmed.1002032 May 31, 2016
12. Fried MW, Shiffman ML, Reddy KR et al. Peginterferon alfa-2a plus ribavarin for chronic hepatitis C virus infection. *NEJM*, 2002, 347: 975-982.
13. Hadziyannis SJ, Sette H, Morgan TR et al. Peginterferon alpha-2a and ribavarin combination therapy in chronic hepatitis C: a randomized study of treatment duration and ribavarin dose. *Ann Intern Med*, 2004, 140(5): 346-355.
14. Kowdley KV, Gordon SC, Reddy KR, et all/ Ledipasvir and sofosbuvir for 8 or 12 weeks for chronic HCV without cirrhosis. *N Engl J Med* 2014: 370: 1879-88.
15. WylesDL, et al. Daclatasvir plus Sofosbuvir for HCV in Patients Coinfected with HIV-1. *N Engl J Med.* 2015 Aug 20;373(8):714-25.
16. Nelson DR, et al. All-oral 12-week treatment with daclatasvir plus sofosbuvir in patients with hepatitis C virus genotype 3 infection: ALLY-3 phase III study. *Hepatology* 2015; 61:1127-35.
17. Poordad F, et al ABT-450/r–Ombitasvir and Dasabuvir with Ribavirin for Hepatitis C with Cirrhosis. *NEJM* 2014;370:1973-1982.
18. Afdhal N, et al. Ledipasvir and sofosbuvir for untreated HCV genotype 1 infection. *NEJM* 2014;370:1889-1898.
19. Afdhal N, et al. Ledipasvir and Sofosbuvir for Previously Treated HCV Genotype 1 Infection. *NEJM* 2014;370:1483-1493.
20. Bourliere M et al. Ledipasvir-sofosbuvir with or without ribavirin to treat patients with HCV genotype 1 infection and cirrhosis non-responsive to previous protease-inhibitor therapy: a randomised, double-blind, phase 2 trial (SIRIUS). *Lancet* ID 2015;15:397-404.
21. Zeuzem S, et al. Sofosbuvir in Genotypes 2 or 3. VALENCE Trial. *N Engl J Med.* 2014;370: 1999-2001.
22. Naggie, ION-4 Ledipasvir-Sofosbuvir for 12 weeks in HCV-HIV Co-infected Patients CROI 2015.

CHAPTER 13

ANTIRETROVIRAL THERAPY AMONG SERODISCORDANT COUPLES

"Couple" is defined as two persons in an ongoing sexual relationship; each of these persons is referred to as a "partner" in the relationship. Whereas "Serodiscordant Couple" means couple in which one partner is HIV-positive and one partner is HIV-negative.

13.1 Prevention of Transmission from the HIV-Positive Partner

ART for prevention of transmission in the HIV-positive partner who is eligible for ART treatment (CD4 < 350 cells/μL)

- ART is strongly recommended as per our current CPG recommendations.
- This also reduces HIV transmission to their unaffected partner.

ART for prevention of transmission in the HIV positive partner with CD4 > 350 cells/μL and who do not have clinical indications for treatment

- ART should be offered to reduce HIV transmission to unaffected partners

The HPTN 052 randomized controlled trial found a 96% reduction in HIV transmission in serodiscordant couples where the partner with HIV with a CD4 count between 350 and 500 cells/μL had started ART early[1].

Treatment should be accompanied by counseling of the couple on the fact that ART is lifelong and the combination of treatment and consistent condom use is likely to offer greater protection than either one alone.

The annual risk of transmission of HIV from an infected partner to an uninfected partner in a serodiscordant relationship can be reduced from 20–25% to 3–7% in programs where condom use is recommended for prevention[2].

13.2 The Benefits of Commencing ART in Serodiscordant Couple

It is possible for couples to remain serodiscordant indefinitely if they consistently practice safer sex using condoms. Combination of treatment and consistent condom usage are likely to offer greater protection.

Treatment for the HIV-positive partner is highly effective in reducing the risk of transmission to the HIV-negative partner as well as to allow safer conception for serodiscordant couples.

REFERENCES

1. Cohen MS, Chen YQ, McCauley M, et al. and the HPTN 052 Study Team. Prevention of HIV-1 infection with early antiretroviral therapy. *N Engl J Med.* 2011;365:493–505.
2. Dunkle KL et al. New heterosexually transmitted HIV infections in married or cohabiting couples in urban Zambia and Rwanda: an analysis of survey and clinical data. *The Lancet*, 2008, 371(9631):2183–2191.

ANTIRETROVIRAL THERAPY FOR ILLICIT DRUG USWERS

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

14.1 HIV Treatment among Illicit Drug Users / IDUs

Methadone and Antiretroviral Therapy

Methadone, an orally administered long-acting opiate agonist, is the most common pharmacologic treatment for opiate addiction. In opioid-dependent people, methadone prevents withdrawal symptoms without producing significant sedation or intoxication. It is the only drug approved as oral substitution therapy in the government hospitals/health centers. Pharmacokinetic interactions of antiretroviral (ARV) agents with methadone are challenges to successful therapy.

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

Table 14.0 • Interactions of Clinical Significance between Methadone and ART [4,5]

Antiretroviral Agent	Effect on Methadone	Methadone Effect on Antiretroviral Agent	Methadone Effect on Antiretroviral Agent Comment
Nucleoside / Nucleotide Reverse Transcriptase Inhibitors (NRTIs)			
Abacavir (ABC)	Methadone clearance ↑ 22%	Concentrations slightly decreased (but not clinically significant)	Patients should be monitored for methadone withdrawal symptoms; dose increase unlikely, but may be required in a small number of patients
Didanosine (ddI)	None	Buffered ddI concentration decreased by 57%	Buffered ddI dose increase may be considered or use EC ddI instead
		EC ddI unchanged	
Emtricitabine (FTC)	No data	No data	
Lamivudine (3TC)	None	None	No dose adjustment necessary
Stavudine (d4T)	None	Reduces d4T AUC and Cmax by ↓23% and 44% respectively	The clinical significance of a change in drug exposure of this magnitude is not certain

Antiretroviral Agent	Effect on Methadone	Methadone Effect on Antiretroviral Agent	Methadone Effect on Antiretroviral Agent Comment
Nucleoside / Nucleotide Reverse Transcriptase Inhibitors (NRTIs)			
Tenofovir (TDF)	None	None	
Zidovudine (AZT)	None	AZT AUC ↑ 29–43%	Monitor for AZT adverse effects, in particular bone marrow suppression (especially anaemia).
Non-nucleoside Reverse Transcriptase Inhibitors (NNRTIs)			
Efavirenz (EFV)	Methadone Cmax ↓ 45% and AUC ↓ 52%	None	Symptoms of withdrawal may develop after 3–7 days, requiring significant increases in the methadone dose
Etravirine (TMC-125)	None	None	No dose adjustment necessary
Nevirapine (NVP)	Methadone AUC ↓ 41%	None	
Protease Inhibitors (PIs)			
Azanavir (ATV)	None	None	if boosted with ritonavir, Methadone AUC ↓ 16%–18%; Opioid withdrawal unlikely but may occur. Adjustment of methadone dose usually not required; however monitor for opioid withdrawal and increase methadone dose as clinically indicated.
Darunavir (DRV)	None	None	
Lopinavir / ritonavir (LPV/r)	None	None	
Integrase Inhibitors			
Raltegravir (RAL)	None	None	No dose adjustment necessary.
Others			
Maraviroc (MRV)	No data–potentially safe	No data – potentially safe	

Buprenorphine and Antiretroviral Therapy

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

Table 14.1 • Interactions of Clinical Significance Between Buprenorphine and ART [4,5]

Antiretroviral Agent	Effect on Burprenorphine	Buprenorphine Effect on Antiretroviral Agent	Buprenorphine Effect on Antiretroviral Agent Comment
Nucleoside / Nucleotide Reverse Transcriptase Inhibitors (NRTIs)			
Abacavir (ABC)	Unknown	Unknown	Potential interaction that may require close monitoring,alteration of drug dosage or timing of administration
Didanosine (ddI)	None	None	No dosage adjustment necessary.
Emtricitabine (FTC)	No data	No data	—
Lamivudine (3TC)	None	None	No dosage adjustment necessary.
Stavudine (d4T)	No data	No data	—
Tenofovir (TDF)	None	None	No dosage adjustment necessary.
Zidovudine (AZT)	None	None	No dosage adjustment necessary.
Non-nucleoside Reverse Transcriptase Inhibitors (NNRTIs)			
Efavirenz (EFV)	Buprenorphine AUC ↓ 50%; norbuprenorphinea AUC ↓ 71%	None	No withdrawal symptoms reported. No dosage adjustment recommended; however, monitor for withdrawal symptoms.
Etravirine (TMC-125)	Buprenorphine AUC ↓ 25%	None	No dosage adjustment necessary.
Nevirapine (NVP)	Methadone AUC ↓ 41%	None	No dose adjustment necessary
Protease Inhibitors (PIs)			
Atazanavir (ATV)	Buprenorphine AUC ↑ 93%; norbuprenorphine AUC ↑ 76%	↓ ATV levels possible	If boosted with ritonavir, Methadone AUC ↓16%–18%;
Atazanavir (ATV) / ritonavir	Buprenorphine AUC ↑ 66%; norbuprenorphine AUC ↑ 105%	None	Monitor for sedation. Buprenorphine dose reduction may be necessary
Darunavir (DRV) / ritonavir	Buprenorphine: no significant effect; norbuprenorphine AUC ↑ 46% and Cmin ↑ 71%	None	No dosage adjustment necessary
Lopinavir / ritonavir (LPV/r)	None	None	No dosage adjustment necessary
Ritonavir (RTV)	Potential for increased buprenorphine effects	No data	Observe; buprenorphine dose reduction may be necessary

Antiretroviral Agent	Effect on Burprenorphine	Burprenorphine Effect on Antiretroviral Agent	Burprenorphine Effect on Antiretroviral Agent Comment
Integrase Inhibitors			
Raltegravir (RAL)	No data– potentially safe	No data– potentially safe	No dose adjustment necessary.
Others			
Maraviroc (MRV)	No data– potentially safe	No data– potentially safe	Observe; buprenorphine dose reduction may be necessary

Subuxone (Buprenorphine/Naloxone) and Antiretroviral Therapy

Buprenorphine–naloxone combines the partial agonist buprenorphine with the opioid antagonist naloxone in a 4:1 ratio. The addition of naloxone deters the abuse by injection of buprenorphine. Subuxone is becoming a popular oral substitution therapy and is available in this country. Naloxone does not have any significant drug interaction with any antiretroviral drugs. Thus, recommendations for buprenorphine and ARVs can be applied when subuxone is used concomitantly with ARVs.

REFERENCES

1. Strathdee SA, Palepu A, Cornelisse PG, Yip B, O'Shaughnessy MV, Montaner JS, et al. Barriers to use of free antiretroviral therapy in injection drug users. *JAMA*, 1998. 280(6):547-9
2. Lucas GM, Mullen BA, Weidle PJ, HaderS, McCaul ME, Moore RD. Directly administered antiretroviral therapy in methadone clinics is associated with improved HIV treatment outcomes, compared with outcomes among concurrent comparison groups. *Clin Infect Dis* 2006;42(11):1636-8
3. Tossonian HK, Raffa JD, Grebely J, Trotter B, Viljoen M, Mead A, et al. Methadone Dosing Strategies in HIV-Infected Injection Drug Users Enrolled in a Directly Observed Therapy Program. *J Acquir Immune Defic Syndr* 2007;45:324–327
4. WHO Guidelines for the Psychosocially Assisted Pharmacological Treatment of Opioid Dependence 2009
5. Guidelines for the use of Antiretroviral Agents in HIV-1 Infected Adults and Adolescent 2012

POST-EXPOSURE PROPHYLAXIS (PEP) FOLLOWING OCCUPATIONAL EXPOSURE

The most common occupational exposure to HIV among Health Care Worker (HCW) is needle stick/sharp injuries. In Malaysia, the Occupational Health Unit in the Ministry of Health has reported an incidence rate of 6.3 needle stick injuries per 1,000 HCWs in 2013.

15.1 Risk for Occupational Transmission of HIV to HCWs

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

15.2 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 fluids that carry significant risk include blood or visibly bloody fluids and other potentially infectious material (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, sweat, nasal secretions, vomitus, urine or feces does not require PEP
4. Advanced HIV infection in the source patient

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

15.3 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 the 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

15.4 Immediate Management

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

15.5 HIV Status of the Source Patient (see Table 15.0 and 15.1)

If the HIV status of the source patient is not immediately available or complete evaluation of the exposure cannot be completed within 2 hours of the exposure, PEP with a 2-drug regime must be immediately initiated while awaiting final decision[3].

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

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

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

15.6 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 15.0 • PEP recommendations when exposed to HIV positive source patient [4]

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

(Adapted from Kuhar DT, Henderson DK, Struble KA et al. Updated US Public Health Service guidelines for the management of occupational exposures to human immunodeficiency virus and recommendations for post exposure prophylaxis, Infection Control and Hospital Epidemiology. 2013; 34 (9); 875-92.

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

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

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

Table 15.1 • Choice of ARV in PEP

2 drug regime	Add for 3 drug regime
Preferred Tenofovir* 300mg od + Emtricitabine* 200mg od **Alternative** Zidovudine 300mg bd + Lamivudine* 150mg bd	**Preferred** Dolutegravir 50mg od/ Raltegravir 400mg bd **Alternative** Lopinavir / Ritonavir 2 tab BD
* Requires dose adjustments if baseline creatinine clearance is <50mL/min Tenofovir should be used with caution in those with renal insufficiency or taking other nephrotoxic drugs	

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

15.8 Timing of Initiation of PEP

All efforts have to be made to initiate PEP as soon as possible, preferably within 2 hours of exposure. Animal studies have shown that PEP is most likely to be effective when initiated within 24-36 hours.[2,3,5] Time duration beyond which PEP should not be administered is not certain. Decisions regarding PEP beyond 36 hours should be made on a case-by-case basis.

15.9 Duration of PEP

Duration: 28 days.[3] Emphasis on adherence to treatment and completion of the course is important to achieve PEP effectiveness. A proactive approach to managing adverse effects will ensure HCWs adhere to PEP.

15.10 Recommended Follow Up of HCW (see Table 15.2)

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

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 HCWs 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, organs, tissue or semen.

Table 15.2 • Monitoring after Initiation of PEP

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

15.11 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 counselling 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 3-5 day supply of PEP to be made available for use especially on weekends and public holidays
4. Funding for ARV drugs.

REFERENCES

1. Bell DM. Occupational risk of human immunodeficiency virus infection in healthcare workers: an overview. Am J Med. 1997;102(suppl 5B):9-15.
2. Cardo DM, Culver DH, Ciesielski C, et al. A case-control study of HIV seroconversion in health care workers after percutaneous exposure. Centers for Disease Control and Prevention Needlestick Surveillance Group. *N Engl J Med.* 1997;337 21):1485-1490.
3. Tsai CC, Emau P, Follis KE, et al. Effectiveness of postinoculation (R)-9-(2-phosphonylmethoxypropyl) adenine treatment for prevention of persistent simian immunodeficiency virus SIVmne infection depends critically on timing of initiation and duration of treatment. *J Virol.* 1998;72(5):4265-4273.
4. Kuhar DT, Henderson DK, Struble KA, et al. Updated US Public Health Service guidelines for the management of occupational exposures to human immunodeficiency virus and recommendations for postexposure prophylaxis. *Infect Control Hosp Epidemiol.* 2013; 34(9):875-892.
5. Shih CC, Kaneshima H, Rabin L, et al. Postexposure prophylaxis with zidovudine suppresses human immunodeficiency virus type 1 infection in SCID-hu mice in a time-dependent manner. *J Infect Dis.* 1991;163(3):625-627.

NON OCCUPATIONAL POST EXPOSURE PROPHYLAXIS (nPEP)

Situations that may prompt request for nPEP include:

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

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

16.2 Initial Assessment for nPEP

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

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

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

Table 16.0 • Estimated per Act Risk of Acquiring Human Immunodeficiency Virus (HIV) from an Infected Source, by Exposure Act[a]

Exposure type	Rate of HIV Acquisition per 10,000 Exposures
Parenteral	
Blood transfusion	9,250
Needle sharing during injection drug use	63
Percutaneous (needle stick)	23
Sexual	
Receptive anal intercourse	138
Receptive penile-vaginal intercourse	8
Insertive anal intercourse	11
Insertive penile-vaginal intercourse	4
Receptive oral intercourse	LOW
Insertive oral intercourse	LOW
Other[b]	
Biting	negligible
Spitting	negligible
Sharing sex toys	negligible

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

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

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

Immediate Management and Assessment of an Individual with Known or Suspected Exposure to HIV (Box 1)

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

Evaluate Exposure. Is nPEP indicated?

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

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

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

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

Table 16.1 • Assessing the Need of nPEP Based on Exposure

Source HIV Status	HIV Positive		Unknown HIV Status	
	HIV VL unknown / detectable (>200 copies/ml)	HIV VL undetectable (<200 copies/ml)	From high prevalence country / risk-group (e.g. MSM)*	From low prevalence country / group
Receptive anal sex	Recommend	Not recommended [%] Provided source has confirmed HIV VL<200c/mL for >6 months	Recommend	Not recommended
Insertive anal sex	Recommend	Not recommended	Consider[†]	Not recommended
Receptive vaginal sex	Recommend	Not recommended	Consider[†]	Not recommended
Insertive vaginal sex	Consider[&]	Not recommended	Consider[†]	Not recommended
Fellatio with ejaculation[‡]	Not recommended	Not recommended	Not recommended	Not recommended
Fellatio without ejaculation[‡]	Not recommended	Not recommended	Not recommended	Not recommended
Splash of semen into eye	Not recommended	Not recommended	Not recommended	Not recommended
Cunnilingus	Not recommended	Not recommended	Not recommended	Not recommended
Sharing of injecting equipment**	Recommended	Not recommended	Consider	Not recommended
Human bite[§]	Not recommended	Not recommended	Not recommended	Not recommended
Needle stick from a discarded needle in the community			Not recommended	Not recommended

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

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

† More detailed knowledge of local prevalence of HIV within communities may change these recommendations from consider to recommended in areas of particularly high HIV prevalence. Co-factors in Box 1 that influence the likelihood of transmission should be considered & Co-factors in Box 1 that influence the likelihood of transmission should be considered‡ PEP is not recommended for individuals receiving fellatio i.e. inserting their penis into another's oral cavity. For individuals giving fellatio PEP is not recommended unless co-factors 1 & 2 in Box 1 are present e.g HIV seroconversion and oropharyngeal trauma/ulceration, see notes in guideline above.

** HIV prevalence amongst IDUs varies considerably depending on country of origin and is particularly high in IDUs from Eastern Europe and central Asia. Region-specific estimates can be found in the UNAIDS Gap Report http://www.unaids.org/sites/default/files/media_asset/05_Peoplewhoinjectdrugs.pdf

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

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

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

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

Flow Chart for Initiation of nPEP:

STEP 1: If nPEP Recommended or Considered

↓

STEP 2: Is Patient Presenting within 72 hours?

↓

STEP 3: Initiate the First Dose of nPEP Regimen

28-DAY REGIMEN — Recommended PEP Regimen:[b], Tenofovir 300 mg PO OD + Emtricitabined 200mg PO OD plus Raltegravir 400 mg PO BD / Dolutegravir 50mg od (See Table 16.6 for alternative regimens)

↓

STEP 4: Baseline Testing

BASELINE TESTING OF EXPOSED PERSON:

- HIV test*
- Pregnancy test for women
- GC/CT NAAT (based on site of exposure)
- RPR for syphilis
- FBC/RP/LFT

* nPEP should not be continued in those who decline baseline HIV testing

+

SOURCE TESTING, if source is available:

- Obtain consent for HIV testing (if source patient's HIV status is unknown)
- Obtain HIV test (preferably with turn around 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 Resultis 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 counselling
- Refer for mental health and/or substance use programs when indicated; consider need for intensive risk reduction counselling services and discuss future use of PrEP with persons with ongoing risk behaviour

[a] Decisions to initiate nPEP beyond 72 hours post-exposure is not recommended[13,28], with the realization of 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 counselling.

[b] If the source is known to be HIV-infected, 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 PEP regimen. Initiation of the first dose of PEP should not be delayed while awaiting this information and/or results of resistance testing. When this information becomes available, the PEP regimen may be changed if needed in consultation with an experienced provider.

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

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

HIV Exposure through Bites (consult Infectious Disease Physician)

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

16.3 Testing for the Exposed Patient

HIV, STI, HBV and HCV screening recommended even if nPEP is declined

16.3.0 Baseline HIV Testing for the Exposed Patient

1. Test for HIV within 3 days of exposure – patients should be tested on the same day and before being given a course of nPEP
2. Do not wait for results to give the initial dose of nPEP
3. If this initial test is subsequently found to be positive, continue nPEP until a confirmatory test assay is viewed
4. Decision to continue treatment will be based on current guidelines, and should be made in consultation with an ID Physician – it is likely now that we would just continue ART and not stop ART in these circumstances where the patient is found to be HIV positive
5. Repeat HIV testing at 4–6 weeks and 3 months after exposure should be performed with laboratory-based test (4th generation HIV test) rather than POC test
6. HIV testing at 4–6 weeks and 3 months is recommended after significant exposures, regardless of whether the individual accepts or declines PEP treatment

16.3.1 Testing for Other STIs

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

16.3.2 Pregnancy Testing and Emergency Contraception

1. All females should be tested for pregnancy
2. Emergency contraception should be discussed and offered

16.3.3 Testing for Hepatitis B Infection (HBV)

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

16.3.4 Testing for Hepatitis C Infection

1. Test for Hepatitis C antibody (Anti HCV)

16.4 Behavioural Intervention and Risk-Reduction Counselling

Recommendations:

1. The clinician or a member of the HIV care team should provide risk-reduction counselling and primary prevention counselling whenever someone presents for nPEP.
2. 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.

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

16.5 Timing of nPEP

1. Ideally should be initiated as soon as possible after exposure, preferably within 24 hours, but can be considered up to 72 hours
2. Duration of nPEP: 28 days

16.6 Recommended Regimes for HIV PEP Following Non-Occupational Exposure

Tenofovir 300 mg PO daily + Emtricitabine 200 mg PO daily
Plus Raltegravir 400 mg PO twice daily / Dolutegravir 50 mg od

Notes:

Rationale for recommended PEP regimen:

- Acts before viral integration with cellular DNA – this may pose a theoretical advantage but is not a reason why integrase inhibitors are used preferentially
- Increased rates of adherence and completion[21, 22]
- Favourable tolerability[23, 24]
- Ease of administration
- Favourable side effect profile,
- Fewer potential drug-drug interactions,

When the source is known to be HIV-infected:

- Past and current ART experience, viral load data, and genotypic or phenotypic resistance data (if available) may indicate the use of an alternative PEP regimen.
- Consult with a clinician experienced in managing PEP.

Renal insufficiency:

- The dosing of tenofovir and emtricitabine/lamivudine should be adjusted in patients with baseline creatinine clearance<50 mL/min.
- Alternative regimen using combivir (zidovudine + lamivudine) may be used.
- Tenofovir should be used with caution in exposed persons with renal insufficiency or who are taking concomitant nephrotoxic medications

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

Alternative regimes

NRTI backbone (2 drugs)	Third agent
Combivir 1 tablet BD (Zidovudine 300mg + Lamivudine 150mg)	Kaletra 2 tablets BD (Lopinavir 200mg + Ritonavir 50 mg)

Notes:

- Three-drug regimen preferred:
  i. Consistent with ARV treatment practices
  ii. 3 drug ARV regimens are associated with better virological suppression than 2 drug regimens in studies of ARVs in treatment of established HIV infection
  iii. Provides greater protection against resistant virus than 2 drug regimens
  iv. Provides consistency across PEP guidelines
- The use of a two-drug regimen would be preferred to discontinuing the regimen completely if tolerability is a concern.

16.7 Follow-Up and Monitoring (refer table 16.2)

Consider re-evaluation within 3 days of the exposure to further clarify the nature of the exposure, review available source person data, evaluate adherence, and monitor toxicities associated with the PEP regimen.

The recommended follow-up and monitoring tests are summarised in Table 16.2

Table 16.2 • Follow-Up and Monitoring

Test	Source	Exposed persons		
	Baseline	Baseline	4–6 weeks after exposure	3 months after exposure
	For all persons considered for or prescribed nPEP for any exposure			
HIV Ag/Ab testing or Ab testing (if Ag/Ab test unavailable)	√	√	√	√[b]
Hepatitis B serology, including: Hepatitis B surface Ag Hepatitis B surface Ab (if resoures available)	√	√	—	√[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).

Modified from Updated Guidelines for Antiretroviral Post exposure 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

REFERENCES

1. Otten RA, Smith DK, Adams DR, et al. Efficacy of postexposure prophylaxis after intravaginal exposure of pig-tailed macaques to a human-derived retrovirus (human immunodeficiency virus type 2). *J Virol* 2000; 74:9771-9775.
2. Smith MS, Foresman L, Lopez GJ, et al. Lasting effects of transient postinoculation tenofovir [9-R-(2 Phosphonomethoxypropyl) adenine] treatment on SHIV (KU2) infection of rhesus macaques. *Virology* 2000; 277:306-315.
3. Van Rompay KK, Miller MD, Marthas ML, et al. Prophylactic and therapeutic benefits of short-term 9-[2(R) (phosphonomethoxy) propyl]adenine (PMPA) administration to newborn macaques following oral inoculation with simian immunodeficiency virus with reduced susceptibility to PMPA. *J Virol* 2000; 74:1767-1774.
4. Connor EM, Sperling RS, Gelber R, et al. Reduction of maternal-infant transmission of human immunodeficiency virus type 1 with zidovudine treatment. Pediatrics AIDS Clinical Trials Group Protocol 076 Study Group. *N Engl J Med* 1994;331:1173-1180
5. Centers for Disease Control and Prevention. Case-control study of HIV seroconversion in health care workers after percutaneous exposure to HIV-infected blood: France, United Kingdom, and United States, January 1988- August 1994. MMWR Morb Mortal Wkly Rep 1995;44:929-933. Available at: www.cdc.gov/mmwr/pdf/wk/mm4450.pdf
6. Schechter M, Do Lago RF, Mendelsohn AB, Moreira RI, Moulton LH, Harrison LH, et al.Behavioral impact, acceptability, and HIV incidence among homosexual men with access to postexposure chemoprophylaxis for HIV.Journal of Acquired Immune Deficiency Syndromes: JAIDS.2004;35(5):519D25
7. Kaplan EH, Heimer R. A model-based estimate of HIV infectivity via needle sharing. *J Acquir Immune Defic Syndr.* 1992; 5:1116-1118.
8. Centers for Disease Control and Prevention. Transmission of HIV possibly associated with exposure of mucous membrane to contaminated blood. MMWR Morb Mortal Wkly Rep 1997; 46:620-623. Available at: http://www.cdc.gov/mmwr/preview/mmwrhtml/00048364.htm
9. Varghese B, Maher JE, Peterman TA, et al. Reducing the risk of sexual HIV transmission: Quantifying the per- act risk for HIV on the basis of choice of partner, sex act, and condom use. *Sex Transm Dis* 2002; 29:38-43.
10 DeGruttola V, Seage GR 3rd, Mayer KH, et al. Infectiousness of HIV between male homosexual partners. *J Clin Epidemiol* 1989;42:849-856.
11. Tovanabutra S, Robison V, Wongtrakul J, et al. Male viral load and heterosexual transmission of HIV 1 subtype E in Northern Thailand. *J Acquir Immune Defic Syndr* 2002;29:275-283.
12. Patterson BK, Landay A, Siegel JN, et al. Susceptibility to human immunodeficiency virus-1 infection of human foreskin and cervical tissue grown in explant culture. *Am J Pathol* 2002;161:867-873.
13. 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
14. LeGoff J, Weiss HA, Gresenguet G, et al. Cervicovaginal HIV-1 and herpes simplex virus type 2 shedding during genital ulcer disease episodes. *AIDS* 2007; 21:1569-1578.
15. Bailey RC, Moses S, Parker CB, et al. Male circumcision for HIV prevention in young men in Kisumu, Kenya: A randomised controlled trial. *Lancet* 2007; 369:643-656.
16. Gray RH, Kigozi G, Serwadda D, et al. Male circumcision for HIV prevention in men in Rakai, Uganda: A randomised trial. *Lancet* 2007; 369:657-666.
17. Beltrami EM, Cheingsong R, Heneine WM, et al. Antiretroviral drug resistance in human immunodeficiency virus-infected source patients for occupational exposures to healthcare workers. *Infect Control Hosp Epidemiol* 2003; 24:724-730.
18. Zamora AB, Rivera MO, García-Algar Ó, et al. Detection of infectious human immunodeficiency type 1 virus in discarded syringes of intravenous drug users. *Pediatr Infect Dis J* 1998;17:655-657.
19. Black RJ. Animal studies of prophylaxis. Am J Med 1997;102:39-44.
20. Van Rompay KK, Berardi CJ, Aguirre NL, et al. Two doses of PMPA protect newborn macaques against oral simian immunodeficiency virus infection. *AIDS* 1998;12:F79-F83.
21. Tsai CC, Emau P, Follis KE, et al. Effectiveness of postinoculation (R)-9-(2 phosphonylmethoxypropyl) adenine treatment for prevention of persistent simian immunodeficiency virus SIVmne infection depends critically on timing of initiation and duration of treatment. *J Virol* 1998;72:4265-4273.
22. Tosini W, Muller P, Prazuck T, et al. Tolerability of HIV postexposure prophylaxis with tenofovir/emtricitabine and lopinavir/ritonavir tablet formulation. *AIDS* 2010;24:2375-2380.
23. Mayer KH, Mimiaga MJ, Cohen D, et al. Tenofovir DF plus lamivudine or emtricitabine for nonoccupational postexposure prophylaxis (nPEP) in a Boston Community Health Center. *J Acquir Immune Defic Syndr* 2008;47:494-499.
24. Mayer KH, Mimiaga MJ, Gelman M, et al. Raltegravir, tenofovir DF, and emtricitabine for postexposure prophylaxis to prevent the sexual transmission of HIV: Safety, tolerability, and adherence. *J Acquir Immune Defic Syndr* 2012;59:354-359.
25. Annandale D, Richardson C, Fisher M, et al. Raltegravir-based post-exposure prophylaxis (PEP): A safe, well-tolerated alternative regimen. *J Int AIDS Soc* 2012;15(Suppl 4):18165. Available at: www.jiasociety.org/index.php/jias/article/view/18165
26. Cardo DM, Culver DH, Ciesielski CA, et al. A case-control study of HIV seroconversion in health care workers after percutaneous exposure: Centers for Disease Control and Prevention Needlestick Surveillance Group. *N Engl J Med* 1997;337:1485-1490.
27. Committee on Pediatric AIDS. Infant feeding and transmission of human immunodeficiency virus in the United States. *Pediatrics* 2013;131;391-396.
28. BASHH UK guideline for the use of HIV post exposure prophylaxis following sexual exposure (PEPSE) 2015

PRE EXPOSURE PROPHYLAXIS (PREP)

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

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

17.1 Who Would You Recommend PrEP To?

17.1.0 Eligibility Citeria for PrEP[5,6]

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

17.1.1 Considerations When the Partner is HIV Positive.

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

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

17.2 Prescribing PrEP

17.2.0 What Should You Prescribe for PrEP? [5]

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

17.2.1 Contraindications for the Use of PrEP

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

17.2.2 Key Efficacy Messages

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

17.2.3 Adverse Effects[8]

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

17.3 Pre-PrEP Counselling & Assessment[5,6]

17.3.0 Education

1. Patient must be made aware of the limitations of PrEP
   - The importance of adherence
   - Lack of protectiveness against STI and pregnancy
   - Doesn't offer 100% protection against HIV
   - It is possible to cycle off oral PrEP when moving out of "seasons of risk" – it is not meant to be lifelong therapy
2. Discussion about start-up syndrome.
   - Such as nausea, abdominal cramping or headache, that are typically mild and self-limited and do not require discontinuing PrEP
   - These symptoms usually resolves after a few weeks of starting
   - A discussion at the beginning may help adherence

3. Discuss adverse effects including long-term safety
    - Include potential but undemonstrated risk of birth defects if taken by a women
4. Confirm schedule for follow-up, with a HIV test at least every 3 months
5. Educate on symptoms of HIV sero-conversion
6. Stress the importance of adherence and adherence support

17.3.1 Assessment

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

17.4 Initial Laboratory Testing

1. Baseline HIV testing – stress the importance of ruling out pre-existing HIV infection
    - Third or fourth-generation HIV test (preferable to use 4th generation lab test)
    - Nucleic Acid Amplification Test (e.g. viral load) for HIV in:

    a. Patients with symptoms of acute infection (influenza or cold-like symptoms)
    b. Patients whose HIV antibody test results are negative but who have reported engaging in unprotected sex with an HIV-infected partner or partner of unknown HIV status within the past month

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

    - Basic metabolic panel – renal function test and liver function test
    - PrEP should not be initiated for patients with a creatinine clearance <50 mL/min
2. Urinalysis
    - Proteinuria can be an early warning sign of tenofovir toxicity
    - Baseline urinalysis should be used to identify any pre-existing proteinuria
3. Serology for Hepatitis A, B and C viruses (Hep A IgG, Hep B sAg , Hep B sAb and Hep B core Ab, Hep C Ab)
    - Hepatitis B vaccination should be provided to susceptible patients who are Hep B sAg and sAb neg

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

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

17.5 Post-PrEP Follow-Up[5,6]

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

17.6 Management of Special Situations

1. Creatinine elevation: consider discontinuing PrEP if creatinine elevation is persistent on a second sample and creatinine clearance <60 ml/min. Recheck creatinine in another 1 to 3 months and PrEP can be restarted if renal function, as measured by CrCl, has returned to >60 ml/min (please notes this is slightly higher than the creatinine clearance for treatment).
2. Seroconversion while receiving PrEP: offer ART as soon as possible without a gap after discontinuation on PrEP even while confirmatory test is underway. A referral to a tertiary center can be done for PrEP providers who are not comfortable starting ART.
3. There are no known interactions between PrEP and hormonal contraceptives.
4. In patients with recurrent HIV exposure requiring nPEP, consider transitioning to PrEP after 28 days of PEP.
5. The use of PrEP in pregnancy and breast-feeding needs to be weighed against the risk of transmitting HIV to the child if the mother becomes infected while pregnant or breast-feeding.

REFERENCES

1. Grant RM, Lama JR, Anderson PL, McMahan V, Liu AY, Vargas L, Goicochea P, Casapía M, Guanira-Carranza JV, Ramirez-Cardich ME, Montoya-Herrera O. Preexposure chemoprophylaxis for HIV prevention in men who have sex with men. N Engl J Med. 2010 Dec 30;2010(363):2587-99.
2. McCormack S, Dunn D. Pragmatic open-label randomised trial of preexposure prophylaxis: the PROUD study. In Conference on retroviruses and opportunistic infections (CROI) 2015 Feb 23 (pp. 23-26).
3. Molina JM, Capitant C, Spire B, Pialoux G, Cotte L, Charreau I, Tremblay C, Le Gall JM, Cua E, Pasquet A, Raffi F. On-demand preexposure prophylaxis in men at high risk for HIV-1 infection. New England Journal of Medicine. 2015 Dec 3;373(23):2237-46.
4. Baeten JM, Donnell D, Ndase P, Mugo NR, Campbell JD, Wangisi J, Tappero JW, Bukusi EA, Cohen CR, Katabira E, Ronald A. Antiretroviral prophylaxis for HIV prevention in heterosexual men and women. New England Journal of Medicine. 2012 Aug 2;367(5):399-410.
5. World Health Organization. Guideline on when to start antiretroviral therapy and on pre-exposure prophylaxis for HIV. World Health Organization; 2015.
6. New York State Department of Health and D Daskalakis. HIV PrEP in the Real World. IAS-USA Perspective. Vol 22 Issue 4. September 2014
7. Cottrell ML, Yang KH, Prince HM et al. Predicting effective Truvada® PrEP dosing strategies with a novel PK-PD model incorporating tissue active metabolites and endogenous nucleotides (EN). AIDS research and human retroviruses. 2014 Oct 1;30(S1):A60-. 7
8. Cooper RD, Wiebe N, Smith N, Keiser P, Naicker S, Tonelli M. Systematic review and meta-analysis: renal safety of tenofovir disoproxil fumarate in HIV-infected patients. Clinical Infectious Diseases. 2010 Sep 1;51(5):496-505.
9. Jones R, Stebbing J, Nelson M, Moyle G, Bower M, Mandalia S, Gazzard B. Renal dysfunction with tenofovir disoproxil fumarate-containing highly active antiretroviral therapy regimens is not observed more frequently: a cohort and case-control study. JAIDS Journal of Acquired Immune Deficiency Syndromes. 2004 Dec 1;37(4):1489-95.
10. Herlitz LC, Mohan S, Stokes MB, Radhakrishnan J, D'Agati VD, Markowitz GS. Tenofovir nephrotoxicity: acute tubular necrosis with distinctive clinical, pathological, and mitochondrial abnormalities. Kidney international. 2010 Dec 1;78(11):1171-7.
11. Nelson MR, Katlama C, Montaner JS, et al. The safety of tenofovir disoproxil fumarate for the treatment of HIV infection in adults: the first 4 years. Aids. 2007 Jun 1;21(10):1273-81.
12. Mulligan K, Glidden DV, Anderson PL, Liu A, McMahan V, Gonzales P, Ramirez-Cardich ME, Namwongprom S, Chodacki P, de Mendonca LM, Wang F. Effects of emtricitabine/tenofovir on bone mineral density in HIV-negative persons in a randomized, double-blind, placebo-controlled trial. Clinical Infectious Diseases. 2015 Aug 15;61(4):572-80.
13. Liu AY, Vittinghoff E, Sellmeyer DE, Irvin R, Mulligan K, Mayer K, Thompson M, Grant R, Pathak S, O'Hara B, Gvetadze R. Bone mineral density in HIV-negative men participating in a tenofovir pre exposure prophylaxis randomized clinical trial in San Francisco. PloS one. 2011 Aug 29;6(8):e23688.

Annex 1 • WHO Clinical Staging of HIV Disease In Adults and Adolescents

CLINICAL STAGE 1

Asymptomatic
Persistent generalized lymphadenopathy

CLINICAL STAGE 2

Unexplained moderate weight loss (under 10% of presumed or measured body weight)
Recurrent upper respiratory tract infections (sinusitis, tonsillitis, otitis media, pharyngitis)
Herpes zoster
Angular cheilitis
Recurrent oral ulceration
Papular pruritic eruptions
Seborrhoeic dermatitis
Fungal nail infection

CLINICAL STAGE 3

Unexplained severe weight loss (over 10% of presumed or measured body weight)
Unexplained chronic diarrhea for longer than one month
Unexplained persistent fever (intermittent or constant for longer than one month)
Persistent oral candidiasis
Oral hairy leukoplakia
Pulmonary tuberculosis (current)
Severe bacterial infections (e.g. pneumonia, empyema, pyomyositis, bone or joint infection, meningitis, bacteraemia, severe pelvic inflammatory disease)
Acute necrotizing ulcerative stomatitis, gingivitis or periodontitis
Unexplained anaemia (below 8 g/dl), neutropenia (below 0.5 x 1.09/l) and/or chronic thrombocytopenia (below 50 x 109/l)

CLINICAL STAGE 4*

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

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

Source: Revised WHO clinical staging and immunological classification of HIV and case definition of HIV for surveillance. 2006

Annex 2 • ARV Combinations that Are Not Recommended

Monotherapy or Dual Therapy	Rapid Development of Resistance
D4T + AZT	Antagonism (reduced levels of both drugs)
D4T + DDI	Overlapping toxicities (pancreatitis, hepatitis, lipoatrophy) Deaths reported in pregnant women
3TC + FTC	Interchangeable, but should not be used together
TDF + 3TC + ABC or TDF + 3TC + DDI	These ARV combinations will increase K65R mutation and are associated with a high incidence of early virological failure
TDF + DDI + any NNRTI	High incidence of early virological failure

Annex 3 • Dosages of Antiretroviral Drugs

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

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

Annex 4 • Dosage Adjustment for ARTS in Renal Impairment

Drug adjustments are based on patient's estimated creatinine clearance

ART	Adjustment for Renal Failure (Crcl) Ml/MIN			Hemodialysis, CAPD	Comments & Dosage for CRRT
LAMIVUDINE	>50 - 90 300mg q24h	10 - 50 50-150mg q24h	<10 25-50mg q24h	HEMO: Dose AD; CAPD: No Data; CRRT: 100mg 1ST day, THEN 50mg/day	
MARAVIROC	300mg bid	No data	No data	Increased risk of side effects if maraviroc+CYP3A inhibitor and CrCl<50	
TENOFOVIR	300mg q24h	300mg q48h	Not recommended	Not recommended	
ZIDOVUDINE	300mg bd	300mg bd	100mg q6-8h	Hemo: Dose for CrCl<10 CAPD: Dose for CrCl<10	

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

List of ARVs with No Dosage Adjustment with Renal Insufficiency	
Efavirenz	Atazanavir
Abacavir	Lopinavir
Efavirenz	Raltegravir

Annex 5 • Severity Grading

GRADE 1	Transient or mild discomfort; no limitation of activity; no medical intervention / therapy required.
GRADE 2	Mild to moderate limitation of activity; some assistance may be needed; no or minimal medical intervention / therapy required.
GRADE 3	Marked limitation of activity; some assistance usually required; medical intervention / therapy required; hospitalization possible.
GRADE 4	Extreme limitation of activity; significant assistance required; significant medical intervention / therapy required; hospitalization or hospice care.

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

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

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