Antiretroviral therapy for HIV infection in adults, adolescents and children

Recommendations for a public health approach

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Health Protection Agency

MINISTRY OF HEALTH

REPUBLIC OF MALDIVES

Foreword

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Chapter: 1 Introduction and Executive summary:

It is estimated that around 35 million persons are living with HIV infection based on UNAIDS estimate in 2013. Among them 4 millions are from South and South East Asia. With the advent of Antiretroviral therapy and with the production of generic antiretrovirals(ARVs) (1,2), 12.9 million persons with HIV disease are receiving Antiretroviral Treatment(ART) (6) . Dramatic decline in morbidity and mortality due to HIV disease had been observed both in the developed and developing countries. (3,4). Robust scale up of ART is happening in South East Asia and in other resource limited settings.(5) and in other lower and middle income countries(LMIC) (6). Recent global update had clearly shown the declining death rate across the region among persons who were on ART.(6).

HPTN052 study had shown 96% reduction in sexual HIV transmission and reduction in incidence of Tuberculosis following ART(7). WHO 2013 ARV guidelines have recommended ART for all serodiscordant couples irrespective of CD4 cell count and for asymptomatics with CD4<500. This guidance will move the eligible numbers who need ART to 25 millions in LMIC. Recent global update had shown reduction in sexual transmission of HIV across the region.(6). When 2013 WHO ARV guidelines are implemented across the regions, greater impact on declining incidence are expected. The major obstacle is identifying individuals with CD4 >350. Data have shown the median CD4 to initiate ARV in low, lower middle and upper middle income countries is

less than 200 (8). Studies have shown mortality rate is higher in the first year after initiation of ART due to the low baseline CD4 cell count (9).

Efforts should be developed in each country on the frequency of HIV testing, which should be cultural specific and based on HIV incidence in different key populations. A recent modeling study done for India have shown voluntary HIV screening among national population every 5yrs and annual screening among high risk population and in high prevalent districts will offer substantial clinical benefit and cost effective (10). Similar exercise should be carried out in each country.

Tuberculosis continues to be major co-factor HIV disease progression in HIV infected persons(11). WHO has recommended IPT which is getting implemented and efforts should be done to make it universal in high endemic regions. WHO 2013 ARV guidelines recommend to initiate ART for all HIV/TB co-infected patients as soon as possible. This will result in reduction in mortality among this population. UNAIDS report have shown declining mortality in HIV/TB co infected patients who are on ART between 2001-2012. (6)

PEARLS/ACTG5175 study carried out in resource limited settings had shown Tenofovir (TDF) containing first line ART is safer and superior as compared to Zidovudine(AZT) containing regimen (12). Also modeling studies have shown Tenofovir is cost effective on a long run as compared to AZT (13).

With the rapid scale up of ARVs, need for 2nd line ARVs are also on the rise. Studies have shown absence of viral load monitoring can lead to immunological and clinical failure and also can jeopardize future regimens due to the accumulation of resistance

mutations. (14,15,16,17). Following this WHO 2013 ARV Guidelines have recommended annual viral load monitoring. Phasing in viral load technology in LMIC is an urgent priority and this needs resources and capacity building. Surveillance of ARV resistance should be carried out periodically in the programs to advise the future guidelines to incorporate newer class of first line ARV regimens.(18,19)

Adherence to antiretroviral therapy and removing stigma are critical to get the maximum efficacy and the effectiveness of benefits.

Studies have shown retention to the care facility is critical for the well being and loss to follow up in programs is very expensive. (20,21)

With the availability of simplified potent ART regimens, persons with HIV live longer. A recently presented cohort study in India had shown significant number of persons were on ART for more than 10years.(22). The major reason for inpatient care in this cohort is due to the non AIDS complications like diabetes, cardiac, renal, liver, malignancy and neurocognitive impairement. A study from Brazil had shown this too. (23).

People living with HIV are now living longer, the impact of expanded HIV treatment, but are also facing non-HIV chronic conditions and experiencing high rates of morbidity related to non-communicable diseases. With these background this guidelines is developed for the management of HIV infection in Maldives.

Chapter 2:

Epidemiology of HIV infection in Maldives

South and South- East Asia region remains second most highly affected in the world. Maldives has a low prevalence of HIV infection (less than 0.1%) (Ref: HPA). The first case of HIV in the Maldives was reported in 1991.

Maldives is a country high risk for a potential concentrated epidemic. Through 2014, 21 HIV-positive cases had been reported among Maldivians (17 male, 4 female) and around 300 or more cases among expatriates. 20 out of 21 cases have been identified through case reporting, one case was identified through the 1st BBS, and majority of the infections were reportedly acquired through heterosexual transmission. However, transmission through blood transfusion is reported. Also, one infant was tested positive for HIV, believed to have infected through vertical transmission. Twelve of the 21 HIV-positive Maldivians died of AIDS, most recent AIDS related death being in 2011. Until recently, in Maldives, HIV infections were imported, however, the most recent infections were local. HIV among key populations was reported in 2011 and 2012; they are from MSM and IDU communities.

. Recent surveys have shown that high risk sex and Injecting drug use practices are on the rise.

There is a genetic predisposition for Thalassemia in Maldivians and hence there are many blood transfusions.

In 2013 alone, 37,778 people were tested for HIV through Provider Initiated Testing (PIT) and Voluntary Counseling and Testing (VCT). Among them a total of 17 persons were confirmed with HIV infection (16 expatriates and 1 Maldivian). Most of these infections are reported in the central region. (HPA). Maldivians frequently travel outside of Maldives for work, business and studies. With the geography and growing tourism in Maldives efforts should be developed for HIV prevention programs in high risk and key populations

to prevent further spread of HIV in Maldives. Strategies to be developed for HIV testing in this population and linkages to care should be planned.

Chapter 3

HIV Testing and Counseling:

HIV testing is the entry point for people to access HIV Treatment, care and prevention services. It is estimated that half of the people living with HIV do not know their status. These numbers are higher in Asia and Africa. People who do not know their status often get tested very late when they are sick with multiple opportunistic infections and immunocompromised .Due to this they can have poor health outcomes and ongoing HIV transmission. Persons who are tested negative should be offered appropriate prevention services including harm reduction for those who use dugs. Retesting should be encouraged at a later time.

Guiding principles*(Adopted from 2013 WHO ARV Guidelines)*

All forms of HIV testing and counselling should be voluntary and adhere to the five C's: consent, confidentiality, counselling, correct test results and connections to care, treatment and prevention services. Mandatory testing is never recommended, whether that coercion comes from a health care provider or from a partner or family member.

The following key principles apply to all models of HIV testing and counselling and in all circumstances:

People receiving HIV testing and counselling must give informed consent (verbal consent is sufficient and written consent is not required) to be tested and counselled.

They should be informed of the process for HIV testing and counselling and their right to decline testing.

HIV testing and counseling services are confidential, meaning that what the HIV testing and counseling provider and the person discuss will not be disclosed to anyone else without the expressed consent of the person being tested. Although confidentiality should be respected, it should not be allowed to reinforce secrecy, stigma or shame. Shared confidentiality with a partner or family members and trusted others and with health care providers is often highly beneficial.

HIV testing and counseling services must be accompanied by appropriate and high- quality pre-test information and post-test counseling. Quality assurance mechanisms and supportive supervision and mentoring systems should be in place to ensure the provision of high-quality counseling.

HIV testing and counseling providers should strive to provide high-quality testing services, and quality assurance mechanisms should be in place to ensure the provision of correct test results. Quality assurance may include both internal and external measures and should include support from the national reference laboratory at IGMH as needed.

Connections to prevention, care and treatment services should include the provision of effective referral to appropriate follow-up services as indicated, including long-term prevention and treatment support.

Quality assurance of both testing and counselling is essential in all approaches used.

The use of rapid HIV diagnostic tests that can be used at point of care has become an important strategy to expand access, increase the return of same-day results and enable appropriate referral and follow-up. The testing algorithm for Maldives is enclosed in Appendix 1.

Who should be tested:

Maldives recommends routine HIV testing and counseling in clinical settings. This is referred to as provider initiated testing and counseling (PITC). This is an efficient way to identify people for treatment. PITC should be offered to adults, adolescents and children attending STI services, TB clinics, medical and surgical services, inpatients, pregnant women in reproductive health services and in services for key population. Partner of serodiscordant couples should be offered annual HIV testing.

HIV testing and counseling is recommended in the community for key population (MSM,IDUs),with linkage to treatment ,care and prevention services.

Partners of antenatal women should be offered HIV counseling and testing.

All infants born to HIV infected mothers will be offered HIV nucleic acid test (HIV DNA/RNA PCR) at 4 to 6 weeks and HIV antibody tests at 18 months of age.

Chapter 4:

Linking people diagnosed with HIV infection to Care and Treatment

In Maldives HIV counseling and Testing are offered in the primary,secondary and tertiary health level. All those tested positive should be linked HIV care and treatment centers. This enables timely initiation of Antiretroviral treatment , access to interventions to prevent further transmission of HIV, prevent other infections and co-morbidities and thereby minimize loss to follow-up.

Before initiation of Antiretroviral treatment the following package of care inventions should be offered:

1) Psychosocial counseling and support
2) Disclosure and partner notification
3) Screening for Tuberculosis and Isoniazid Preventive Therapy (IPT)
4) Screening for symptom driven opportunistic infections, co-infections and management
5) Co-trimoxazole prophylaxis
6) Preventing common fungal infections and Malaria
7) VDRL Screening, treatment and prevention of sexually transmitted infections
8) Screening for cervical cancer
9) Screening for HBsAg and HCV

10) Selected vaccine preventable diseases
11) Counseling on nutrition, hygiene and safe water
12) Family planning and reproductive health services
13) Prevention of Mother to Child HIV transmission
14) Needle and Syringe programs for people who inject drugs
15) Baseline CD4, CBC, LFT, RFT, Blood sugar, Lipid profile, HIV antibodies to rule out HIV-1 and HIV-2, pregnancy test in women of child bearing age

Preparing people living with HIV for Antiretroviral Treatment:

Before initiating ART, a detailed discussion with persons with HIV about their willingness and readiness to initiate ART, the ARV regimen, dosage, scheduling, benefits, common side effects to ARVs, and required followup and monitoring visits should be done both by the counselor and the treating physician.

Chapter: 5

Antiretroviral Therapy: When to start ART

Early treatment initiation is associated with clinical and HIV prevention benefits, improving survival and reducing the incidence of HIV infection at the community level. The 2013 W H O Guidelines Development Group recommends that national HIV programs provide ART to all people with a confirmed HIV diagnosis with a CD4 count of 500 cells/mm^3 or less, giving priority to initiating ART among those with severe/advanced HIV disease or a CD4 count of 350 cells/mm^3 or less. It is also recommended to initiate ART in people with active TB disease and HBV coinfection with severe liver disease, all pregnant and breastfeeding women with HIV, all children younger than five years living with HIV and all individuals with HIV in serodiscordant relationships, regardless of CD4 cell count .

HPTN052 study had shown initiating ART at CD4 cell count of 350-550 has resulted in prevention of HIV transmission ,Tuberculosis and other clinical events.(Ref) and cost effective to the programs (Ref). Cohorts studies have shown initiating treatment at a CD4 >500 has resulted in better treatment outcomes (Ref).

Since the prevalence of HIV in Maldives is too low and with the vision of treatment as prevention and to avoid loss to follow-up, it is recommended to initiate ART to all HIV infected individuals diagnosed with HIV infection in Maldives.

Table:

Summary of recommendations on when to start ART in adults, adolescents, pregnant and breastfeeding women and children

Population	**Recommendation**
Adults and adolescents >10yrs old	Initiate ART irrespective of CD4 cell count and clinical stage *Priority to those with CD4< 500, WHO stage 3 or 4,active TB,HBV/HCV coinfection,pregnant and breast feeding women with HIV, HIV positive individual in a serodiscordant partnership*
Children >5 yrs old	Initiate ART irrespective of CD4 cell count and clinical stage *Priority to those with CD4< 500, WHO stage 3 or 4,active TB*
Children 1-5 yrs old	Initiate ART irrespective of CD4 cell count and clinical stage
Infants* < 1yr old	Initiate ART irrespective of CD4 cell count and clinical stage

**Initiate ART in all HIV-infected children below 18 months of age with presumptive clinical diagnosis of HIV infection if early infant diagnosis is not done*

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What ART regimen to start (first line ART):

Once daily, less toxic, fixed dose combination antiretroviral regimen is recommended for all persons initiating ART for HIV-1 infection. PEARLS study carried out in resource limited settings clearly showed Tenofovir containing (TDF/FTC/EFV) is superior to Zidovudine containing (AZT /3TC/EFV) regimen in terms of long term toxicity. (Ref) Hence for Maldives it is recommended TDF+3TC/FTC+EFV is recommended as the initial regimen to start in adults, adolescent (10-19yrs) and in pregnant women. Safety of Tenofovir(TDF) is not proved in children less than <10yrs of age. Hence for Maldives, Abacavir (ABC) oontaining ABC+3TC+EFV is recommended for children between 3-10yrs of age. Children with less than 3 yrs have high viral load and hence more potent Lopinavir (LPVr) containing (ABC/3TC/LPVr) is recommended to initiate.

HIV-2 infection

HIV-2 prevalence low in Asia. Since HIV-2 is naturally resistant to NNRTI(NVP,EFV), persons mono infected HIV-2 and co-infected HIV-1 and HIV-2 , should be initiated with LPVr containing (TDF/ABC/AZT+3TC/FTC+LPVr) antiretroviral regimen. Atazanavir is not recommended.

Table:

Summary of first line ART regimens for Adults, Adolescents, Pregnant and breast feeding women and Children with HIV-1 infection

Population	Preferred first line regimen	Alternate first line regimen
Adults (including pregnant and breast feeding women, adults with TB and HBV coinfection)	**TDF+3TC/FTC+EFV**	**ABC+3TC+EFV** **TDF+FTC+NVP** **AZT+3TC+EFV** **AZT+3TC+NVP**
Adolescents (10-19 yrs) and >35kg	**TDF+3TC/FTC+EFV**	**ABC+3TC+EFV** **TDF+FTC+NVP** **AZT+3TC+EFV** **AZT+3TC+NVP**
Children 3-10yrs and <35kg	**ABC+3TC+EFV**	**ABC+3TC+NVP** **AZT+3TC+EFV** **AZT+3TC+NVP** **TDF+FTC+NVP**

Children< 3yrs	**ABC/AZT+3TC+LPVr**	**ABC+3TC+NVP** **AZT+3TC+NVP**

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Laboratory monitoring before and after initiation of ART:

Clinical and Laboratory assessment is important in assessing individuals before ART is initiated and then monitoring their treatment response and possible toxicity of ARVs. The recommended laboratory tests at baseline and for monitoring are summarized in the table below:

Table

Lab assays	Baseline	Frequency on followup
CBC	+	1st month,every 6 months
LFT	+	1st month, every 6 months
S.Creatinine*	+	1st month, every 6 months
CD4	+	Every 6 months. After virological suppression**, annualy
HIV RNA	-	6th month, if suppressed* annualy

Blood sugar	+	Every 12 months
Lipid profile	+	Every 12 months

**Use the estimated glomerular filtration rate at baseline before initiating TDF*

****** *Recent meta analysis shows reducing the frequency of CD4 after virological suppression is cost effective.*

Monitoring response to ART and the diagnosis of treatment failure:

Viral load is recommended as the preferred monitoring approach to diagnose and confirm ARV treatment failure. Treatment failure is defined by a persistently detectable viral load exceeding 400 copies/ml (that is, two consecutive viral load measurements within a three-month interval, with adherence support between measurements) after at least six months of using ARV drugs. Viralload should be tested at 6 months after initiating ART and if suppressed to < 400 copies/ml then every 12 months to detect treatment failure.

If the viral load is not available, CD4 count and clinical monitoring can be used to diagnose treatment failure. Virological failure occurs first, followed by immunological failure and then clinical failure. Based on modeling studies the duration between these can be 6 months to 2 years. If the failed ARV regimen is not switched following virological failure, resistance mutations can get accumulated and can jeopardize future treatment options including ATVs preserved for 2nd line and Third line.(ref,ref,ref)

Graph explaining the dynamics of Treatment failure:

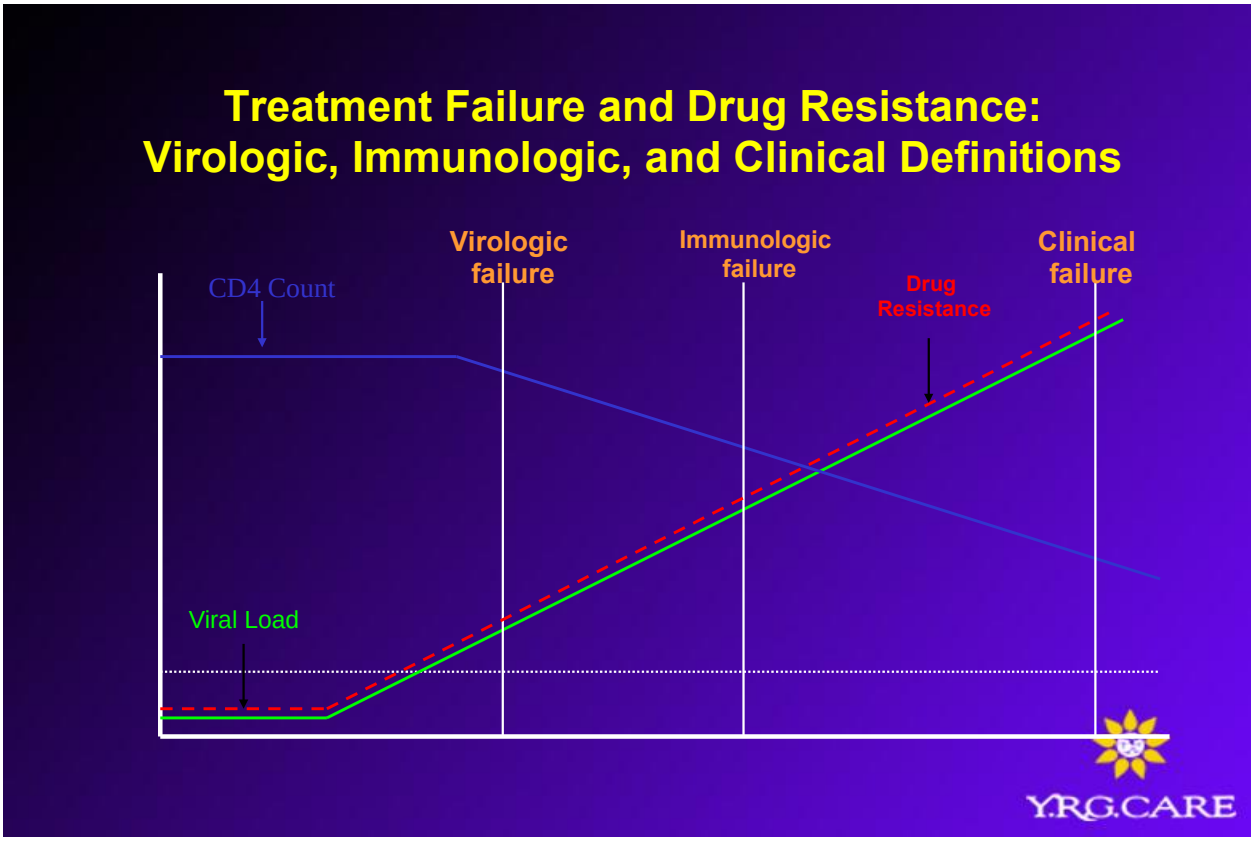

Table: WHO definitions of clinical, immunological and virological failure for the decision to switch ART regimen

Failure	Definition
Clinical failure	*Adults and adolescents* New or recurrent clinical event indicating severe immunodeficiency (WHO stage 4 conditions) after 6 months of ART *Children* New or recurrent clinical event indicating advanced immunodeficiency (WHO stage 3 or 4 except TB) after 6 months of ART
Immunological failure	*Adults and adolescents* CD4 falls to the baseline Or Persistent CD4 levels below 100 cells/mm *Children* Persistent CD4 <200 cells or < 10% in

	younger than 5yrs old and persistent CD4<100 cells in children older than 5 yrs.
Virological failure	Plasma viral load > 400 copies/ml after 6 months of ART on 2 consecutive viral load measurements within 3 months interval with adherence counseling

Chapter: 8

What ART regimen to switch to (second-line ART)

Due to the HIV resistance mutations pattern following the recommended first line ART, patients with treatment failure should be switched to a ritonavir boosted PI+ two NRTI combination ART as the preferred second line ART in adults, adolescents and in children when NNRTI containing regimens are used for the first line ART. In children using a PI-based regimen for first line ART, switching to NNRTI or maintaining the PI regimen is recommended.

Table: **Summary of preferred second line ART regimen for Adults, Adolescents, pregnant women and children:**

Population	**Second line ART regimen** ***Preferred***	**Second line ART regimen** ***Alternative***
Adults, adolescents(>10yrs old),pregnant and breast feeding women	AZT+3TC+ATVr	AZT+3TC+LPVr *RAL+ LPVr or ATVr **TDF+3TC+ATVr
Children (if NNRTI-based first line ART was used)	ABC+3TC+LPVr (<6 yrs old) ABC+3TC+ATVr (>6yrs old)	
Children (if PI based first line ART regimen was used and < 3yrs old	Continue the first line PIr based regimen and improve adherence and monitor	AZT+3TC+NVP

	Viral load	
Children (if PI based first line ART regimen was used and >3yrs old)	AZT or ABC+ 3TC+ EFV	ABC+3TC+NVP TDF+3TC+EFV

**Patients who are anemic or intolerant to AZT, a combination of Raltegravir(RAL)+PIr can be used.*
*** If AZT or d4T was used in the first line ART regimen at the time of Treatment failure.*
**** TDF should be continued in the secondline ART regimen if the patients are coinfected with HBV if there are no adverse effects*

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Third-line ART

Patients virologically failing while on boosted Protease inhibitor containing second line ART regimen should be switched to a Third-line regimen which include drugs with minimal cross-resistance to previously used regimens.

The preferred third line regimen should include ritonavir boosted Darunavir+ Integrase inhibitor (Raltegravir or Dolutegravir*) + Second generation NNRTI (Etravirine).

Maraviroc, a CCR5 antagonist is recently available in developing countries like India for thirdline ART regimen but the use of this drug requires HIV tropism assay which is not locally available.

Patients on a failing second line regimen with no new Thirdline ARV options should continue the tolerated Second line regimen.

** when available.*

Chapter: 10

ARV toxicities:

Antiretroviral therapy is life long and hence safety and tolerabilty of these ARV drugs are important to prevent morbidity and poor adherence to Antiretrovirals. Clinical and laboratory monitoring should be done to identify early adverse effects of ARVs and appropriate drug substitution should be done.

Table : Types of toxicities associated with first-, second-,third-line ARV drugs

ARV Drug	Major type of toxicitiy	Risk factor	Suggested management
ABC	Hypersensitivity reaction	Presence of HLA-B*5701 gene	If ABC is being used in first-line ART, substitute with TDF or AZT If ABC is being used in secondline ART, substitute with TDF or AZT which ever has not been used in first line.
ATV/r	Electrocardiographic abnormalities (PR interval prolongation) Indirect	Pre-existing conduction disease Concomitant use of other drugs that may prolong the PR interval Underlying hepatic disease	LPV/r or DRV/r. If boosted PIs are contraindicated &

	hyperbilirubinaemia (clinical jaundice)	HBV and HCV coinfection Concomitant use of hepatotoxic drugs	NNRTIs have failed in first-line ART, consider integrase inhibitors
	Nephrolithiasis and risk of prematurity	Risk factors unknown	
AZT	Anemia, neutropaenia, myopathy, lipoatrophy or lipoatrophy	Baseline anemia or neutropaenia CD4 count ≤200 cells/mm3	If AZT is being used in first-line ART, substitute with TDF or ABC If AZT is being used in second-line ART, substitute with Integrase inhibitor
	Lactic acidosis or severe hepatomegaly with Steatosis	BMI >25 (or body weight >75 kg) Prolonged exposure to nucleoside analogues	
d4T (currently this ARV is phased out from guidelines)	Peripheral neuropathy, lipoatrophy or lipodystrophy	Older age CD4 count ≤200 cells/mm3 Concomitant use of isoniazid	If d4T is being used in first-line ART, substitute with TDF or ABC If d4T is being used in second-line ART (after TDF or ABC are used in first-line ART), substitute with AZT. *Before substitution plasma viral load should be done and should be suppressed.*
	Lactic acidosis or severe hepatomegaly with steatosis, acute pancreatitis	BMI >25 (or body weight >75 kg) Prolonged exposure to nucleoside analogues	
EFV	Persistent central nervous system toxicity(such as abnormal dreams, depression or mental confusion)	Depression or other mental disorder (previous or at baseline) Daytime dosing	Reduce the dose of EFV to 400mgs in non TB and non pregnant women. Alternatively NVP can be used. If the person cannot tolerate either NNRTI, use boosted PIs
	Hepatotoxicity	Underlying hepatic disease – HBV and HCV coinfection Concomitant use of hepatotoxic drug	
	Convulsions	History of seizure	

	Hypersensitivity reaction, Stevens-Johnson syndrome Male gynaecomastia	Risk factors unknown	
LPV/r	Electrocardiographic abnormalities (PR and QT interval prolongation, torsades de pointes)	People with pre-existing conduction system disease Concomitant use of other drugs that may prolong the PR interval	If LPV/r is used in first-line ART for children, use an age-appropriate NNRTI (NVP for children younger than 3 years and EFV for children3 years and older). ATV can be used for children older than 6 years If LPV/r is used in second-line ART for adults, use ATV/r or DRV/r.
	QT interval prolongation	Congenital long QT syndrome Hypokalaemia Concomitant use of drugs that may prolong the QT Interval	
	Hepatotoxicity	Underlying hepatic disease HBV and HCV coinfection Concomitant use of hepatotoxic drugs	
	Pancreatitis	Advanced HIV disease	
	Risk of prematurity, lipodystrophy or metabolic syndrome, dyslipidemia or severe diarrhoea	Risk factors unknow	
NVP	Hepatotoxicity	Underlying hepatic disease HBV and HCV coinfection Concomitant use of hepatotoxic drugs CD4 >250 cells/mm3 in women CD4 >400 cells/mm3 in men First 2 weeks of therapy (if lead-in dose is not used)	EFV. If the person cannot tolerate either NNRTI, use boosted PIs
	Severe skin rash and hypersensitivity	Risk factors unknown	

	reaction (Stevens-Johnson syndrome)		
RAL	Rhabdomyolysis, myopathy, myalgia	Concomitant use of other drugs that increase the risk of myopathy and rhabdomyolysis	Limited options are available Dolutegravir when available
TDF	Tubular renal dysfunction, Fanconi syndrome Decreases in bone mineral density	Underlying renal disease, Older age BMI <18.5 (or body weight <50 kg) Untreated diabetes mellitus Untreated hypertension Concomitant use of nephrotoxic drugs or a boosted PI History of osteomalacia and pathological fracture Risk factors for osteoporosis or bone loss	If TDF is being used in first-line ART, substitute with ABC or AZT If TDF is being used in second-line ART (after d4T /AZT use in firstline ART), substitute with Integrase inhibitor. ABC can be used instead but in the presence of severe Thymidine mutations to AZT/d4T, ABC efficacy is inferior
	Lactic acidosis or severe hepatomegaly with steatosis	Prolonged exposure to nucleoside analogues Obesity	
	Exacerbation of hepatitis B (hepatic flares)	Discontinuation of TDF due to toxicity	Use alternative drug for hepatitis B treatment (such as entecavir)

**Before any drug substitution for chronic toxicity make sure patients are virologically suppressed*

Drug-Drug interactions

It is very important to be aware of all the drugs that the patient with HIV is taking when initiating ART and also when adding new drugs in patients taking ART. There are several key drug interactions.

A key consideration for managing coinfection with TB and HIV is contraindication of drug combination that includes rifampicin and PIs. When people coinfected with TB and HIV are receiving a boosted PI, rifampicin may need to be substituted with rifabutin. If rifabutin is not available, LPV/r and SQV/r can be used for the duration of TB treatment. In case if it is not possible to avoid Protease inhibitor another option is to use non rifampicin based ATT and better to consult TB expert eg- streptomycin + ETH + INH + Ofloxacin initial phase followed by INH + ETH for 8 months.

AZT has been associated with an increased risk of anaemia and hepatic de-compensation with Ribavirin and peg interferon alpha-2a used for treating HCV. AZT in people co-infected with HCV and HIV may need to be switched to TDF.

NVP may decrease the concentrations of Itraconazole and ketoconazole to sub therapeutic levels when they are used together so when treating fungal infections fluconazole could be used to ensure adequate treatment.
Most of the ARVs mainly EFV decreases methadone concentration leading to withdrawal symptoms and increasing risk of relapse to opioid use so dose adjustment is required. Similar result is expected with Buprenorphine also.

ARVs (especially some NNRTIs and RTV boosted PIs) may alter the effectiveness of mainly oestrogen containing hormonal contraceptives. In such case consistent use of condom or other contraceptive method recommended.

Concomitant use of boosted PIs and NNRTI with antihistamine (eg: astemizole and terfenadine) are associated severe and life threatening reactions like cardiac arrhythmias. Alternative agents like loratidine and cetirizine are preferred. Atazanavir

has fatal interaction with proton pump inhibitors (PPIs) and should never be used concomitantly.

Boosted PIs may lead to increased concentrations of lovastatin & simvastatin which may increase the risk of developing serious adverse events such as myopathy (including rhabdomyolysis). Alternative dyslipidemia agents should be used to prevent severe toxicity among people with HIV.

Table : Key ARV drug interactions and suggested management

ARV drug	Key interactions	Suggested management
AZT	Ribavirin and peg-interferon alfa-2a	First-line: substitute AZT with TDF Second-line: substitute AZT with Integrase inhibitors
Boosted PI(ATV/r, LPV/r)	Rifampicin	Substitute rifampicin with rifabutin Adjust the PI dose or substitute with three NRTIs (for children)
	Lovastatin and **simvastatin**	**Use an alternative dyslipidaemia agent (for example pravastatin)**
	Estrogen-based hormonal contraception	Use alternative or additional contraceptive Methods
	Methadone and buprenorphine	Adjust methadone and buprenorphine doses as appropriate
	Astemizole and terfenadine	Use alternative antihistamine agent
	TDF	Monitor renal function
EFV	Amodiaquine	Use an alternative antimalarial agent
	Methadone	Adjust the methadone dose as appropriate
	Estrogen-based hormonal Contraception	Use alternative or additional contraceptive Methods
	Astemizole and terfenadine	Use an alternative anti-histamine agent
NVP	Rifampicin	Substitute NVP with EFV
	Itraconazole and ketoconazole	Use an alternative antifungal agent (for example fluconazole)

Chapter: 11

Antiretroviral Therapy among persons co-infected with Tuberculosis

Tuberculosis is one of the most common opportunistic infection among persons with HIV disease in developing countries. Tuberculosis accelerates HIV disease progression and vice versa.

STRIDE, SAPIT and CAMELIA studies were carried in resource limited settings to answer the question When to initiate ART in the context of active Tuberculosis. These studies showed delaying the initiation of ART among persons with HIV and TB with CD4 less than 50 cells resulted in increased mortality. (Ref,Ref,Ref).

Hence it is strongly recommended to initiate ART among persons with HIV and TB within 2 weeks as soon as the anti-Tuberculosis therapy is tolerated.

Efavirenz containing first line ART regimen is recommended along with anti-Tuberculosis therapy with Rifampicin. Everyday TB therapy is recommended and the duration of TB treatment is 6-9 months.

In adults and adolescents, among patients on second line Atazanavir/r (ATVr) containing therapy, Rifabutin 150mgs once daily containg TB treatment is recommended. If Rifabutin is not available, Rifampicin can given with Lopinavir (LPVr) containing second line regimen and the dosage of Lopinavir (LPVr) should be doubled to achieve the required therapeutic concentration. Close followup for the liver toxicity is stongly recommended.

Table: Recommended ART regimens for children who need TB treatment:

Population	**ART regimen**
Younger than 3yrs	Two NRTIs+ NVP 200mgs/m2 or Triple NRTIs (AZT+3TC+ABC)
3yrs and older	Two NRTIs+ EFV
Children initiated on LPVr based regimen	Triple NRTI (AZT+3TC+ABC) or Substitute NVP for LPVr or Continue LPVr, consider adding Ritonavir(RTV) to achieve the full

	therapeutic dose

Chapter: 12

Immune reconstitution inflammatory syndrome (IRIS)

IRIS is a spectrum of clinical signs and symptoms thought to be associated with immune recovery brought by a response to ART. It is a widely recognized phenomenon that occurs among 10-30% of the people initiating ART, usually within the first 4 -8 weeks after initiating therapy (Ref,Ref).nIt may present in two different ways:paradoxical IRIS, when an opportunistic infection diagnosed before ART initially responds to treatment but then deteriprates after ART strats; or unmasking IRIS, in which initiating ART triggers disease that is not clinically apparent before ART. It should be considered only when the presentation cannot be explained by a new infection or drug toxicity.

The clinical spectrum is diverse and IRIS has been reported for many different infections, tumors and non-infectious conditions (Ref,Ref). The most serious and life-threatening forms of paradoxical IRIS are for TB,Cryptococcal meningitis,Kaposis sarcoma and herpes zoster. BCG vaccine associated IRIS may occur in infants. A low CD4 cell count (<50 cells) at ART initiation, disseminated opportunistic infections or tumors and a shorter duration of therapy for opportunistic infections before ART start are the main risk factors. (Ref,Ref). IRIS is managed by the continuation of the effective treatment for the opportunistic infections or tumors. Tapering doses of Prednisolone can be used for 3 to 4 weeks. Effective ART should not be interrupted for IRIS management. The patients should be counseled and reassured to prevent discontinuation of or poor adherence to ART.

The most important steps to reduce the development of IRIS include: earlier diagnosis of HIV and initiation of ART before a CD4 decline to acquire opportunistic infections; improving the screening for opportunistic infections before ART especially for TB and Cryptococcus and optimal management of opportunistic infections before initiation of ART. Timing of ART in people with opportunistic infections requires balancing a greater risk of IRIS after early initiation against continuing high mortality if ART is delayed.

Randomized clinical trials have shown early initiation of ART among patients with TB prevented mortality (Ref, Ref). On the other hand randomized trials had shown in the context of cryptococcal meningitis, delaying the initiation of ART upto 6 weeks had resulted in reduction in mortality due to Crypto IRIS. (Ref)

Chapter: 13 Prevention of Co-infections and co-morbidities:

Various co-infections, comorbidities and other health conditions are common among people living with HIV. This chapter briefly summarizes the prevention of co-infections and comorbidities.

Co-trimoxazole preventive therapy:

Cotrimoxazole preventive therapy results in prevention of pneumocystis pneumonia, toxoplasmosis and bacterial infections. Also reduction in incidence of Malaria has been observed among patients who are cotrimoxazole preventive therapy.

Table: Criteria for initiating and discontinuing cotrimoxazole preventive therapy

Age	**Criteria for initiation**	**for discontinuation**
HIV-exposed infants	In all starting at 4-6 weeks	Untill the risk of HIV

	after birth	transmission ends or HIV infection is excluded
<1 year	In all	Untill 5 yrs of age regardless of CD4 and clinical symptoms
1-5 yrs	In all	Never
> 5 yrs, adults, adolescents, pregnant women	CD4<350 or WHO 3 or 4 stage irrespective of CD4	When viral load is suppressed and the CD4>350 after 6 months of ART

Isoniazid preventive therapy (IPT):

Adults, adolescents living with HIV should be clinically screened for Tuberculosis. Those don't have current cough, fever, weight loss, night sweats are unlikely to have active disease. A chest X-ray should be done to rule out TB. These individuals who have no TB should be offered Isoniazid preventive therapy (IPT) for 6 months irrespective of CD4 cell count. Also those on ART and previously treated for TB and pregnant women should receive IPT.

A TST is not a requirement for initiating IPT.

Children living with HIV who are more than 12 months of age and who are unlikely to have active TB on symptom based screening and have no contact with a TB case should receive 6 months of IPT (10mgs/kg/day).

Children living with HIV who are less than 12 months of age, only those who have contact with a TB case and who are evaluated for TB should receive 6 months of IPT if the evaluation shows no TB disease.

All children with HIV after successful completion of TB treatment should receive isoniazid for additional 6 months.

Cryptococcal infection: (Refer : Crypto WHO Guidelines)

Cryptococcal meningitis is one of the most important opportunistic infection and a major contributor to mortality before and after ART is initiated.

Use of routine serum or plasma Cryptococcus neoformans antigen (CrAg) screening in ART naïve adults, followed by pre-emptive antifungal therapy (fluconazole) if CrAg – positive and asymptomatic to reduce the development of cryptococcal disease is recommended.

Routine use of antifungal (fluconazole) primary prophylaxis for cryptococcal disease in adults living HIV with a CD4 count less than 100 cells and who are Cr-Ag negative is recommended prior ART initiation.

These are not recommended in adolescents and children with a CD4 cell count of less than 100 cells prior to ART initiation.

Among persons with HIV with a recent diagnosis of cryptococcal meningitis, ART initiation should be deferred upto 4 to 6 weeks to avoid the serious risk of IRIS.

Hepatitis B and C:

All patients with HIV should be screened at baseline for HBV and HCV. Persons who are negative to HBV should be vaccinated. ART should be initiated in all those co-infected with HBV and HCV.

Patients co-infected HIV and HBV who have failed TDF containing first line ART should continue TDF in the second line regimen if there are no adverse effects to TDF.

For the management of HCV, there are newer oral drugs recently approved for use and refer WHO treatment guidelines for HCV (ref).

Cervical cancer:

Cervical cancer is a preventable disease and curable if diagnosed and treated early. Women living with HIV have a higher risk of pre-cancer and invasive cervical cancer. The risk and persistence of HPV infection increases with decreasing CD4 count and increasing viral load. Invasive cervical cancer is a WHO HIV clinical stage 4 condition. Women with HIV should be closely followed for evidence of pre-cancerous changes in the cervix and should be offered annual pap smear screening. Immediate management

for pre-cancerous and cancerous lesions should be provided. Routine HPV vaccination is recommended for HIV-infected women.

Vaccines for people living with HIV:

All persons with HIV should be assessed for eligibility for vaccination and should be offered. HIV exposed infants and children and young adults should receive all vaccines under routine vaccination as per the national immunization schedule. Thse with severe immunosuppression may be at higher risk of complications from live vaccines. Inactivated vaccines are more effective among people receiving ART and those without immunosuppression.

Chapter: 14

Screening for non communicable diseases (NCDs):

People living with HIV are at increased risk of developing a range of noncommunicable diseases (NCDs) including cardiovascular disease, diabetes,renal disease,bone disease, chronic lung disease and cancers. With ART people are living longer and experiencing NCDs associated with ageing and inflammation. Annual screening for blood sugar and lipids are recommended. Dietery counseling, smoking cessation, promoting exercise, monitoring blood pressure are recommended to prevent morbidity due to NCDs.

Chapter: 15

Nutritional support and counseling:

Nutritional assessment (anthropometry clinical and dietary assessment), counseling and support should be offered to all adults, adolescents and children with HIV. Malnourished HIV patients may require food supplements. Weight loss or failure to regain or maintain a healthy weight should trigger further assessment and appropriate intervention.

Chapter: 16

Adherence to ART and Retention in care:

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

Multiple factors related health care delivery systems, the medication and the persons taking ARVs may affect the adherence to ART.

The individual patient factors include

1) forgetting doses

2) being away from home

3) changes in daily routine

4) depression

5) other illness

6) lack of interest or desire to take medications

7) Substance or alcohol abuse

The medication related factors include

1) intolerance to ARVs and adverse effects
2) complexiy of dosing regimens
3) pill burden
4) dietary resptrictions

The Health care system factors include

1) requiring persons with HIV to visit health services frequently to receive care and to collect ARVs
2) traveling long distances to reach health services
3) bearing the costs of care and ARVs

Lack of clear information or instruction on medication, limited knowledge on the course of HIV infection and treatment and adverse effects can all be barriers to adherence to ART. Uninterrupted ARV drug supply and continuity of care are essential for perons to adhere to their medication. Absence of supportive environments for people

living with HIV and due to HIV related stigma and discrimination, adherence to ART may be challenging.

Adherence issues in special population:

The pregnancy and postpartum period presents significant biological, social and economic challenges that may affect treatment adherence.

Adherence challenges faced by adolescents include pill burden, stigma and fear of disclosure,concerns about safety of medications, adverse effects and peer pressure.

The limited choice of pediatric formulations, poor palatability of liquid formulations, high pill or liquid volume burden, larger pill size, frequent dosing requirements, dietary restrictions, loss of primary caregiver, difficulties in swallowing tablets and adverse effects may all affect adherence. (Ref,Ref).

Adherence to ART is complicated by mental health disorder that results in forgetfulness. Studies have shown depression with low levels of adherence to ART.

Individuals with substance use disorders may have poor adherence to ART. In sveral settings at risk population including sex workers, MSM,transgender people and people who inject drugs face multiple challenges including stigma and discrimination and they need appropriate psychosocial support to improve ART adherence.

Interventions to increase ART adherence:

1) ART should be initiated only when the patient is ready to take and patient education regarding the ARVs is essential.

2) Counseling about ART adherence should be done before initiation of ART and at every visit.
3) Family members can be involved to act as DOTs provider with the consent of the patient.
4) Mobile SMS reminders can be done to alert ART adherence and clinic visits with the consent of the patient.
5) Close follow up by counselors should be made mandatory.
6) Use of less toxic Fixed dose combination (FDC) ART regimen is strongly recommended.
7) Pharmacy refill records, Adherence self-report and pill counts should be maintained to assess and counsel ART.

Chapter: 17

Retention in care:

Studies have shown loss to follow up is expensive to the programs. Retaining people with HIV is essential for optimal health outcomes. Program should develop measures to avoid loss to follow up. Higher loss to followup is seen in programs before initiation of ART.

1) ART and related diagnostics and services should be offered free of charge
2) Decentralize ART
3) Schedule facility visits
4) Reduce waiting time at the facility level

5) Create stigma free environment at the clinics for the patients to seek care
6) Optimize ARV supply management systems to forecast, procure and deliver to avoid stock outs
7) Implement systems for patient monitoring and patient tracking systems.
8) Use mobile SMS to alert clinic follow up visits .
9) Integrate and provide linkage to other health services for TB, STI, reproductive health and non Communicable diseases.

Chapter: 18

Antiretroviral Therapy for prevention:

Prevention of Mother to Child HIV transmission:

All pregnant women and their partners should be offered HIV testing and counseling. HIV positive pregnant mothers should be counseled to initiate ART as soon as possible once the diagnosis is confirmed. The choice ART regimen is indicated in Chapter:6.

Viral load should be done at 6th month after initiation of ART and if suppressed advised to do a repeat viral load 2 to 3 weeks before delivery to ensure virological suppression in pregnant women. If the viral load is suppressed, it is recommended to do normal

delivery procedures. The effective antiretroviral therapy should be continued after delivery in the mothers.

The mothers should be counseled regarding feeding practices. Pros and cons of breast feeding should be explained to the mothers. If the mothers choose to provide infant formula, counseling on safe water and hygenic preparation of infant formula should be done.

Infants should receive 4-6 weeks of prophylaxis with once daily Syp.Nevirapine or twice daily Syp.AZT. Maternal HIV antibodies can persist in infants upto 18 months. Early infant diagnosis (EID) should be carried out at 4 to 6 weeks after birth (Annex). HIV antibody assay should be done after 18 months to rule out HIV infection in the infants.

Post Exposure prophylaxis (PEP):

All health care workers should adopt universal precautions to prevent blood borne associated infections like HIV, HBC, HCV and others. Post exposure prophylaxis should be offered for occupational and non-occupational (sexual) exposure to HIV to reduce the likelihood of acquiring HIV infection. The injured site should be washed with clean running water. The following Antiretroviral regimen should be offered

Exposure	**Regimen**
Intact skin	Do not offer
Mucous membrane	TDF+FTC+Raltegravir Alternate:

	TDF/AZT+FTC/3TC+ATVr/LPVr/DRVr/EFV* **EFV should be used only if other drugs are not available*
Percutaneous	TDF+FTC+Raltegravir Alternate: TDF/AZT+FTC/3TC+ATVr/LPVr/DRVr/EFV* *EFV should be used only if other drugs are not available*

The recommended duration of post exposure prophylaxis for HIV infection is 28 days and the first dose should be offered as soon as possible within 72 hours after exposure. The same recommendation is offered for rape and following unprotected sexual exposure for the negative partner of a serodiscordant couple. HIV antibody test should be done at the baseline, 6th week, 12th week and 4th month to rule out HIV infection. During the post-exposure prophylaxis period safe sex with partners, avoiding blood donation and avoiding breast feeding should be done.

Oral pre-exposure prophylaxis (PrEP):

Oral pre-exposure prophylaxis of HIV (PrEP)is the daily use of ARVs by HIV-uninfected people to block the acquisition of HIV. Clinical trials of daily oral PrEP with TDF+FTC have shown evidence of effectiveness with serodiscordant heterosexual couples (ref), men and transgender women who have sex with men (ref), high risk heterosexual couples (ref) and people who inject drugs (ref).

Feasibility and acceptability studies are needed in Maldives for the planning of implementation of this recommendation.

ART for serodiscordant couples:

HPTN 052 study demonstrated the effectivess of ART in HIV prevention among the serodiscordant couples(ref). Following this all the infected partner of the serodiscordant couples should be initiated on ART irrespective of the CD4 cell count or clinical stage.

Chapter 19

Implementation Science Research:

An electronic database capturing demographics, date of HIV diagnosis,presenting complaints , opportunistic infections, co-morbidities, baseline lab investigations and clinical and laboratory details on follow up visits including occurrence of adverse events and NCDs with dates should be developed and implemented. Adherence rates should also be captured in this database. This database can be used for cohort analysis and to understand toxicity pattern in the local Maldivian population.

Barriers associated with HIV testing in different population should be studied.

Conclusion:

Anriretroviral Treatment has resulted in decrease in morbidity and mortality globally. There is declining incidence of HIV and testing strategies to be developed and implemented to identify HIV infected individuals with high CD4 cell count to link and retain in care in Maldives. Sustainability of ARV programs will require forward looking policies, more effective and innovative approaches, together with further investments. Efforts should be in place to prevent the transmission of ARV resistance strains. Viral load monitoring and adherence counseling will assist this. With increasing NCDs in the HIV infected population , programs should integrate HIV care in health service delivery to prevent and manage NCDs. ARVs for treatment and prevention are a powerful tool towards ending the HIV epidemic. HIV might be positioned within the post-2015 development agenda, with a vision of 'ending the AIDS epidemic'

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Ref To add

Annexes

Annex 1: HIV testing Algorithm in Maldives

Annex 2: Algorithm for early infant diagnosis

Annex 3: Dosages of recommended ARVs for adults and adolescents

Annex 4: Dosages of recommended ARVs for Children

Annex 5: Common Adverse effects of ARVs

Annex 6: Patient monitoring data: HIV care and ART patient monitoring and data recording forms