Management of HIV Disease

National Treatment Guidelines

May 2005

Department of Public Health
Ministry of Health
World Health Organization
Republic of Maldives

Contents

1. Introduction:

The introduction of Highly Active Antiretroviral Therapy (HAART) has led to dramatic reductions in HIV related morbidity and mortality in developed countries and also in developing countries. (ref). Although the treatments are not a cure and present new challenges with respect to side effects and drug resistance, they have improved the quality of life of persons with HIV/AIDS. HIV disease is now perceived as a chronic manageable disease like diabetes and hypertension.

Unfortunately 90% of the 42 million people living with HIV reside in developing countries where antiretroviral therapy is not universally available. WHO estimated that by the end of 2004, some 6 million people in developing countries were in immediate need of antiretroviral therapy. However, only about 400,000 persons were being treated. WHO calls for unprecedented action to ensure that by the end of 2005 at least 3 million people in need of ART will have access to it.

This Treatment Guideline is a cornerstone of the WHO 3 by 5 plan. This guideline was prepared considering the expertise, infrastructure and resources available in the health care sector.

2. Epidemiology of HIV infection in Maldives:

The first case of AIDS was diagnosed in 1981 in the United States among homosexual men who had developed Pneumocytis carini pneumonia. United Nation AIDS programme (UNAIDS) has projected that 36- 42 million person with HIV infection were living by the end of 2004 globally. Among them 6- 8 million were in South and South East Asia. UNAIDS had also predicted that there 14,000 new HIV infections everyday and majority of them occurred in developing countries.

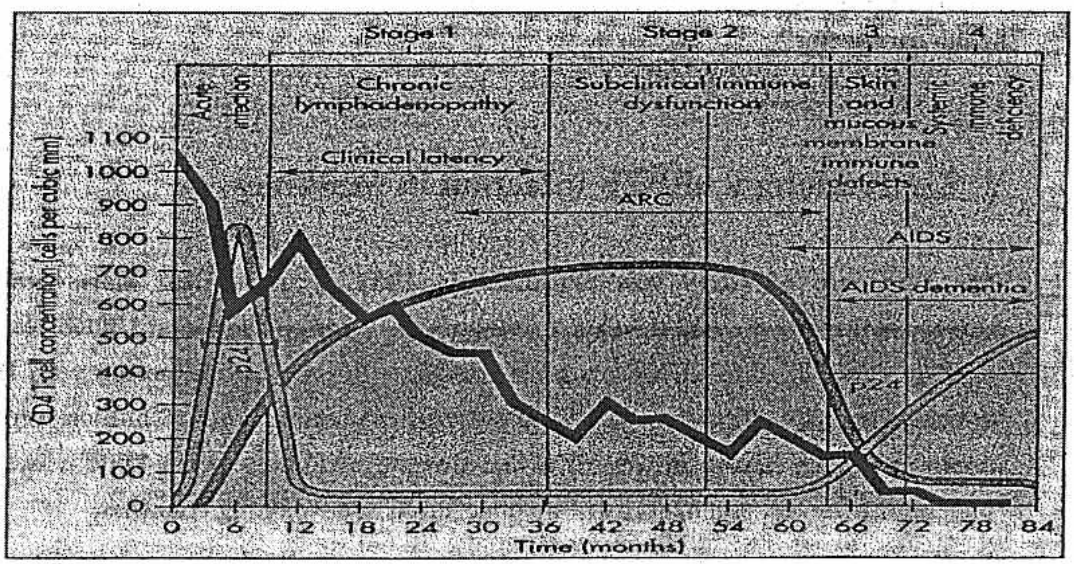
The first case of HIV infection in Maldives was reported in 1991 (ref). Untill end of Sep 2004, 13 HIV-positive cases have been reported among Maldivians and 141 cases among expatriates. Of the 13 HIV-positive cases reported among Maldivians,

ten were sailors, two were the spouses of these sailors and one was a resort worker. 11 of the thirteen cases were men. All infections were acquired through heterosexual route. 9 were dead. So far only one person is receiving highly active antiretroviral therapy.

Although the prevalence of HIV infection is very low in Maldives at present, with high number seamen who are away from families for prolonged periods and with the increasing number of injecting drug users, efforts should be done to prevent future explosion of HIV epidemic in Maldives.

3. Diagnosis of HIV infection:

HIV can be diagnosed during acute infection by nucleic acid- based test (PCR for pro-viral DNA and RT-PCR for viral RNA), P24 antigen testing or culture. Antibodies to HIV are detectable within 4 to 6 weeks after infection. Once antibodies appear in the blood, they persist for the lifetime (Fig).

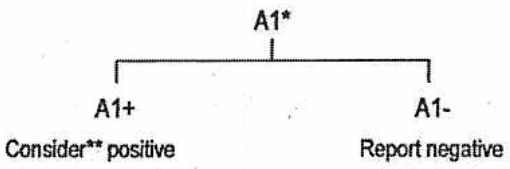


The antibodies to HIV are detected by ELISA, Rapid tests or by Western Blot. Prior to antibody testing counseling to assess the risk factor and the date of exposure should be done.

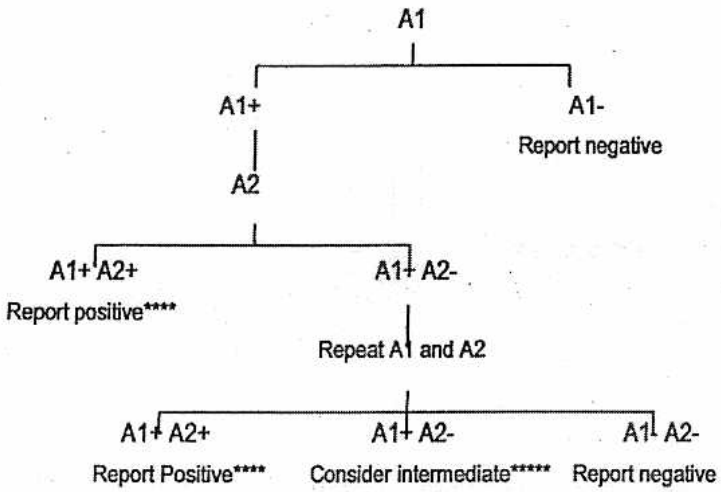
WHO HIV testing strategies (adapted from WHO-Guidelines for HIV Diagnosis and monitoring of Antiretroviral Therapy)

Figure 1: Schematic representation of WHO HIV testing strategies

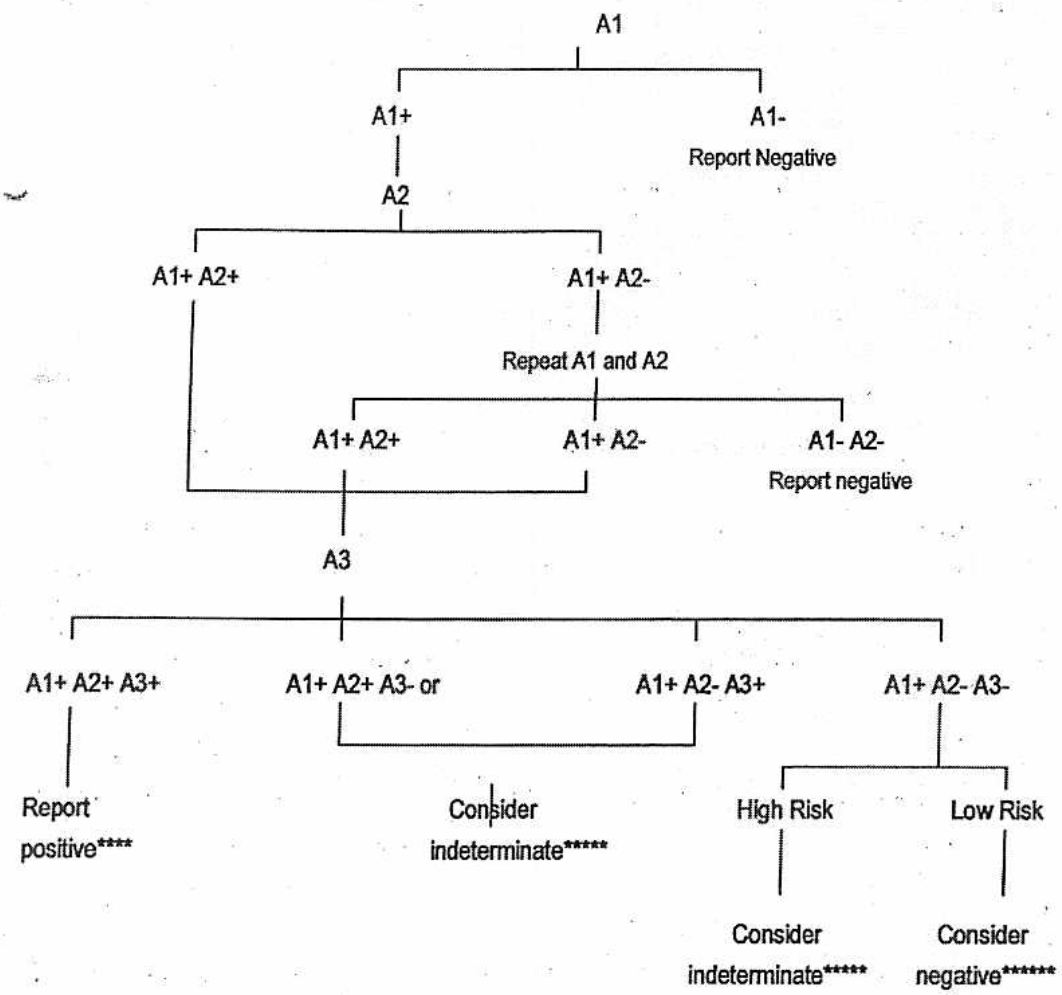
Strategy - 1: Transfusion/transplant safety Surveillance



Strategy 2: Surveillance Diagnosis



Strategy 3 : Diagnosis



*Assay A1, A2 and A3 represent three different assays.

**Such a result is not adequate for diagnostic purposes: use strategy II or III. Whatever the diagnosis, donations which were earlier reactive should not be used for transfusion or transplant.

***Report: result may be reported.

****For newly diagnosed individuals a positive result should be confirmed on a second specimen.

*****Testing should be repeated on a second specimen taken after 14 days.

******Result is considered negative in the absence of any risk of HIV infection.

The follow-up sample from patients with indeterminate result should be collected two weeks after the first sample collection. If the second sample also shows indeterminate result, it should be tested by a confirmatory assay (e.g.- Western Blot). However, if the confirmatory test fails to resolve the sero-diagnosis, follow up testing should be undertaken at four weeks, three months, six months, and 12 month. After 12 months, such indeterminate results should be considered negative.

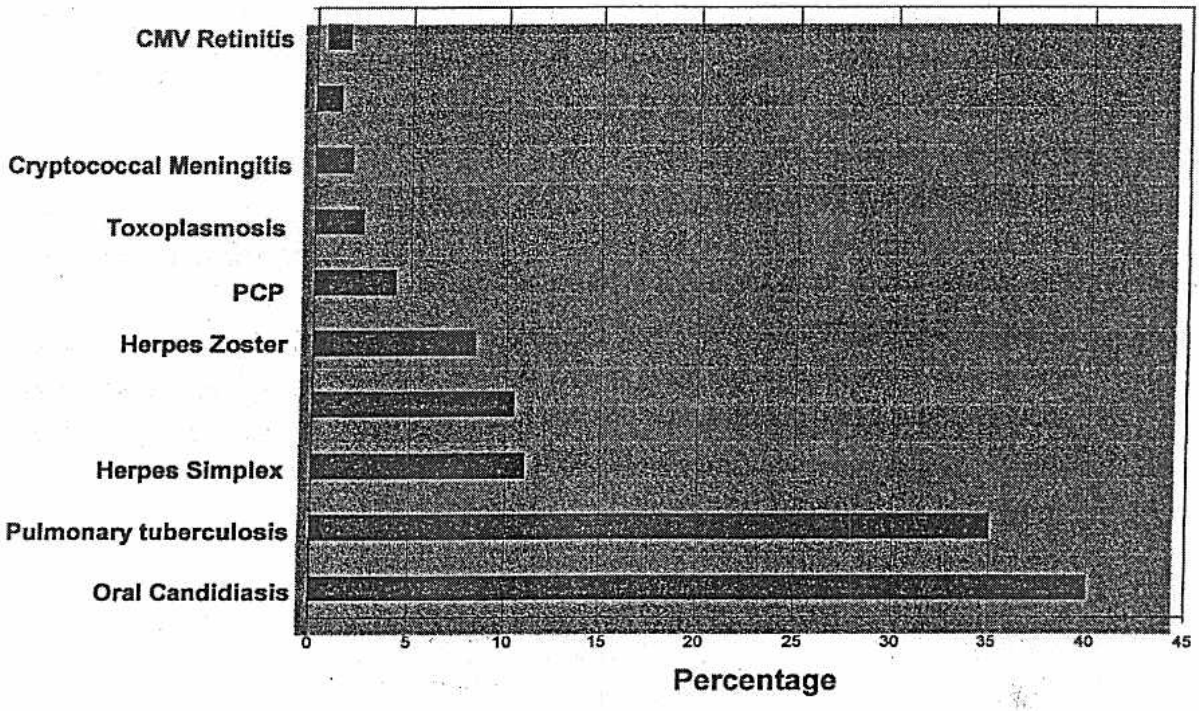
4. Natural history of HIV disease:

The natural history of untreated HIV infection begins with viral transmission. After 2-3 weeks of HIV acquisition, the 20-30% % of the infected individuals experience acute retroviral syndrome. This illness is characterized by Arthralgia, body pain, sore throat, and fever with or without skin rash. This event is accompanied by high plasma viremia and decline in CD4 cell counts. Several times this illness goes unnoticed. This syndrome is also called primary infection or seroconversion illness. Clinical recovery occurs within 2-4 weeks which is accompanied by reduction in plasma viremia and CD4 count recovery. At this time the infected individuals will be asymptomatic and this period can last up to 8 years without any signs of HIV disease. HIV RNA concentrations in plasma show an initial burst during acute infection and then decline to a set point as a result of seroconversion and immune response. With continued infection HIV level increases and results in decline in CD4 cell count.

HIV disease is marked by progressive decline in the number of circulating CD4+ T helper cells which leads to immunological decline and death from opportunistic infections and neoplasm (Fauci AS *et al*, 1996). Clinical course and pattern of Opportunistic infections varies from patient to patient and from country to country (d'Arminio Monfote A, *et al* 1992; Mohar A, *et al* 1992; Bem C, *et al* 1993; Kumarasamy N, *et al* 1995). Median survival after AIDS diagnosis before antiretroviral therapy era was 12 to18 months (Mocroft A, *et al* 1996). Specific AIDS defining illnesses, CD4 cell counts and Plasma Viral Load predict survival of persons with HIV disease (Friedland GH, *et al* 1991; Petruckevitch A, *et al* 1998).

The spectrum of opportunistic infection in Maldives is not studied and reported currently. The most common opportunistic infections in the neighboring country of India studied in a large series of patients are Oropharngeal candidiasis and Tuberculosis. (Fig).

Spectrum of Opportunistic Infections among Patients with HIV in India (Kumarasamy N, et al, Clinical Profile of HIV in India. Indian J Med Res. 2005 Apr;121(4):377-94.)



Late stages of HIV disease is characterized by a CD4 cell count less than 200 cells/cubicmm and the occurrence of opportunistic infections, malignancies, wasting and neurological complications. With effective chemoprophylaxis for opportunistic infections (Appendix) and use of antiretroviral therapy there is a delay in the onset of AIDS, a longer survival and a change in the pattern of opportunistic infections in the developed World (Porter K, *et al* 1996; Brodt HR, *et al* 1997)

Table1 Correlation between CD4 cell count and occurrence of Opportunistic infections: (Arch Intern Med 1995; 155:1537)

CD4 cell count (cells/cubic mm)	HIV associated conditions
>500	Acute retroviral syndrome Persistent Generalized Lymphadenopathy Myopathy Aseptic menigitis
200-500	Pulmonary Tuberculosis Oropharyngeal candidisis Herpes zoster OHL ITP Cervical cancer
<200	Miliary/extrapulmonary TB Pneumocystis carini pneumonia Disseminated Histoplasmosis and coccidioidomycosis Wasting Peripheral Neuropathy HIV-associated Dementia NHL
<100	Cryptococcosis Toxoplasmosis Chronic Cryptosporidiosis Microsporidiosis Esophagial candidiasis Disseminated herpes simplex PML
<50	Disseminated CMV Disseminated MAC CNS lymphoma

Diagnosis, management and prophylaxis of the common opportunistic infections were given in the Appendix.

5. Principles of Antiretroviral Therapy:

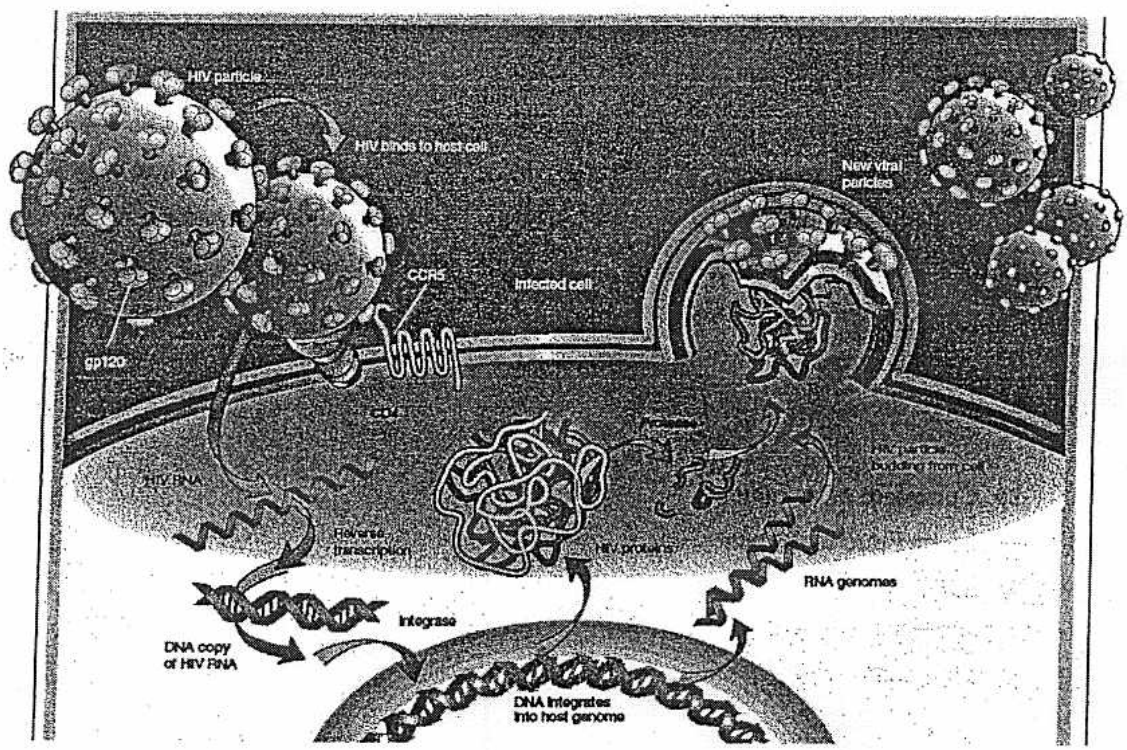
Antiretroviral drugs acts by disrupting the lifecycle of HIV by inhibiting either reverse transcriptase, an enzyme involved in the conversion of HIV RNA to proviral DNA (reverse transcriptase inhibitors) or protease, an enzyme involved in the maturation of HIV virions (protease inhibitors). Also antiretroviral drugs are available which can block the fusion of HIV with the receptors on the T lymphocytes and they are called fusion inhibitors

Various Antiretrovirals approved by FDA:

nRTIs	NNRTIs	NtRTIs	PIs	Fusion inhibitors
Zidovudine(AZT) Lamivudine(3TC) Didanosine(ddI) Stavudine(d4T) Abacavir(ABC) Emitricitabine(FTC) Zalcitabine(ddC)	Nevirapine(NVP) Efavirenz(EFV) Delaviridine(DLV)	Tenofovir(TDF)	Ritonavir(RTV) Indinavir(IDV) Saquinavir(SQV) Nelfinavir(NFV) Amprenavir(APV) Atazanavir(ATV) Lopinavir/(LPV/r) Ritonavir	Enfuvirtide((T20)

nRTIs: Nucleoside reverse transcriptase inhibitors
NNRTIs: Non nucleoside reverse transcriptase inhibitors
NtRTIs: Nuclotide reverse transcriptase inhibitors
PIs: Protease inhibitors

Figure:



Goals of antiretroviral therapy:

1) Maximal and durable suppression of viral load
2) Restoration and/or preservation of immunologic function
3) Reduction of HIV related morbidity and mortality
4) Improvement of quality of life of HIV infected persons.

To achieve the goals, antiretroviral therapy should be administered lifelong.

6. When to start Antiretroviral therapy in adults and adolescents:

Before initiating antiretroviral therapy a detailed clinical examination should be done. All symptoms associated opportunistic infections and HIV associated conditions should diagnosed and should be treated. A detailed history regarding the past medical illness and details regarding any previous use of antiretroviral medications should be obtained. The weight of the patient should be recorded.

The following laboratory investigations should be carried out baseline before initiating antiretroviral therapy.

1) Complete blood count
2) Liver Functions tests
3) RPR
4) HBV,HCV serology
5) CD4 cell count

A detailed counseling on the medications and the importance of adherence to antiretroviral drugs should be discussed with the patients.

Criteria to initiate antiretroviral therapy:

1) Symptomatic with any of the HIV associated conditions (WHO- Stage 3 and 4) irrespective of CD4 cell count
2) Asymptomatic if CD4 between 200 and 350- Observe the patient and closely monitor. If they develop any HIV associated conditions in the follow up period or if there is a decline in CD4 cell count, then initiate ARVs
3) Asymptomatic and if the CD4 cell count is less than 200 cells/micro lit

Before initiating ARVs, discuss with the patient that the therapy is lifelong. Initiate ARVs only if the medications are available or affordable for a prolonged period.

7. Recommended first line ARV regimens

While choosing the first line ARV regimens the following factors should be considered:

- ☐ Potency
- ☐ side-effect profile
- ☐ laboratory monitoring requirements
- ☐ patient adherence
- ☐ coexistent conditions
- ☐ pregnancy
- ☐ use of concomitant medications
- ☐ prior exposure to ARVs given for prophylaxis or treatment
- ☐ availability and cost

With all these factors in background the following combination is suggested for the first line management:

2 NRTI + 1 NNRTI

Stavudine (d4T)*				**Nevirapine(NVP)**
or	**+ Lamivudine(3TC)**	**+**	**or**	
Zidovudine(AZT)				**Efavirenz(EFV)**

NNRTI does act against HIV-2. In patients with HIV-2 one of the following protease inhibitors should be given instead of NNRTI.

Lopinavir/Ritonavir or Saquinavir/Ritonavir or Indinavir/Ritonavir

Only the boosted protease inhibitor with Ritonavir is recommended.

Efavirenz is teratogenic and hence should not be used in pregnant women.

Among patients who are on Rifampicin containing anti-TB treatment, Efavirenz is preferred instead of Nevirapine. If Nevirapine is used close monitoring with LFT is needed since the risk developing hepatitis is higher among persons receiving both Nevirapine and Rifampicin.

Emitricitabine (FTC) and Tenofovir (TDF) are newer drugs and can be used in the first line when increasingly available.

Mono and dual therapies should not be used. AZT should not be combined with d4T because of antagonism between them. Didanosine (ddI) and stavudine (d4T) combination is no longer recommended due to the toxicity. Stavudine (d4T) is better tolerated than Zidovudine (AZT) and also can be used in persons with anemia.

*However d4T on a longer usage can be associated with lipoatrophy and, peripheral neuropathy, metabolic abnormalities and lactic acidosis. But still d4T is recommended as the first line regimen due to availability and low cost. Tenofovir (TDF) should be considered instead of d4T as first line drug if available.(ref)

8. Toxicities of Antiretrovirals:

Toxicities of antiretrovirals can occur within days of initiating the therapy and also causes severe toxicities after a longer usage

a) Initial problems tolerating the therapy

AZT: causes nausea and a headache. You don't need to change the drugs. Reassurance and symptomatic management can be provided. If severe you can change to d4T.

EFV: causes sleep disturbances and night dreams. Patients should avoid alcohol while on EFV therapy. If severe, EFV can be switched to NVP

NFV: causes diarrhea, Rule out other causes of diarrhea. Nutritional counseling and anti-motility drugs can be given

b) Hypersensitivity reactions:

NVP: Nevirapine can cause hypersensitivity reactions in the form of rash and if severe Stevens Johnsons Syndrome can occur. To avoid this Nevirapine should be initiated with 200 mgs once daily for 14 days along with other ARVs and the dose should be escalated to 200 mgs twice daily. If severe rash or SJS occurs, NVP should be discontinued and should be switched to EFV.

Abacavir: Can develop hypersensitivity reactions. Never rechallenge with abacavir if hypersensitivity reactions occur.

c) Immune reconstitution syndrome:

Immune reconstitution syndrome (IRS) have been documented to complicate the management of patients who have initiated ARV treatment (ref,). IRS have been described for mycobacterial infections (both Mycobacterium tuberculosis and Mycobacterium avium complex), Pneumocystic carinii pneumonia, toxoplasmosis, cryptococcal infection and PML. (ref3-ref9). An IRS is characterized by high fever and worsening of the clinical manifestations of the OI.

Successful management has included continuing ARV treatment with the addition of anti-inflammatory agents including corticosteroids. (Prednisolone for 3 -4 weeks starting with 40 mgs PO once daily and the dose should be tapered)

Severe inflammatory reactions have also been reported after HAART was started in patients with an established OI. The high prevalence of MTB in Asian countries suggests that TB IRS will be frequent. Previous study from the region shows the incidence of immune reconstitution syndrome among persons co infected HIV and TB and initiating HAART was 15.2 cases per 100 patient-years. The median days to the development of clinical IRS was 42 days (range 10-89) days. (ref)

Hence it is recommended to initiate HAART for patients with HIV and TB after TB therapy is tolerated (between 2 weeks and 2 months) to avoid IRS.

d) Chronic toxicities:

AZT: causes anemia. If severe, AZT can be switched to d4T.

NVP: causes hepatitis. If NVP containing HAART is given along with Rifampicin containing ATT, the risk to develop hepatitis is high. Hence close monitoring with LFT is needed.

ddI: Causes pancreatitis. Serum amylase and pancreatic lipase along with ultra sonogram will be helpful to diagnose this condition. ddI should be switched. d4T and 3TC can also precipitate this condition and hence should be given if pancreatitis develops.

d4T: Can cause severe peripheral neuropathy. Also with a prolonged usage d4T can cause metabolic complications and fat redistribution syndrome in the form of lipoatrophy. If very severe for cosmetic reasons d4T should be changed.

Protease inhibitors: causes metabolic abnormalities and dyslipidemia. PIs also cause lipodystrophy.

Indinavir: causes renal stones and hence adequate hydration is needed to avoid this.

e) Drug-Drug interactions:

Along with anti-TB drugs, antifungals and other symptomatic medications many ARVs causes drug interactions and hence close monitoring for these toxicities should be done. Protease inhibitors when given with Rifampicin can cause fatal hepatitis. (Described in chapter 12-C). Drug interactions of ARVs with other commonly used drugs are provided in Appendix.

9. Criteria to switch ARVs:

If patients develop toxicities due to ARVs as described in chapter 8, only that particular drug should be changed.

If patients develop failure, then all the drugs should be switched 3 newer drugs.

Definition of treatment failure:

Clinical signs

Occurrence of new OI or malignancy

Recurrence of prior opportunistic infection

Onset or recurrence of WHO Stage III disease conditions

CD4 cell criteria

Return of CD4 to pre-treatment level

> 50% decrease of CD4 during treatment without other concomitant infection

If any patients meet any one of the above criteria, then all the drugs should be switched.

Currently ARV resistance testing is not available in Maldives. When available genotyping results will be used to switch therapy

10. Clinical and Laboratory monitoring:

All patients who are on ARVs should be monitored clinically and with laboratory investigations.

After initiating on ARVs, it is advised to review the patients after 2 weeks. At this visit, adherence to medications and any early toxicities should be looked for.

Thereafter patients should be monitored preferably every month clinically. At each clinical visit, occurrence of new OIs and/or worsening of existing OIs should be looked for. Clinical examination should also be directed to look for toxicities as described in Chapter 8.

The following laboratory investigations should be done .

Investigations	Baseline	1st month	3rd month	6th month	Every 6 months
Complete Blood Count including Haemoglobin	X		X	X	X
Haemoglobin		X (If on AZT)			
Liver function tests (Bilirubin and SGPT)	X	X (If on NVP)	X	X	X
CD4	X		X	X	X

If any patients develop symptoms of OIs while on ARV therapy then symptom directed investigations to diagnose OIs should be done.

The following investigations can be done to diagnose toxicities if suspected.

Serum amylase and lipase, Serum Lactate, Renal function tests, Blood sugar, Lipid profile, Ultra sonogram abdomen.

Currently viral load is not recommended to monitor patients. When available, will be used to monitor patients.

11. Second line ARV regimens in the event of treatment failure:

The criteria described in chapter 8 should be used to switch ARVs in the event of failure. The following drugs can used as the second line of regimen:

First line		Second line
d4T or ZDV		**TDF or ABC**
+		**+**
3TC	**Change to**	**ddI**
+		**+**
NVP or EFZ		**LPV/r or SQV/r or IDV/r**

12. ARV Regimen

a) ARV regimens in pregnant women:

ARVs should be initiated in pregnant women based on the eligibility criteria for ART. Efavirenz should be avoided because of its potential for teratogenicity. If nevirapine is contraindicated or has developed toxicity then ritonovir boosted Saqunavir or Nelfinavir is preferred.

Indications for initiation of ART during pregnancy

- WHO stage 4 disease irrespective of CD4 cell count
- WHO stage 3 HIV disease and CD4 <250*
- Asymptomatic if CD4<200

Recommended initial regimen

Zidovudine(AZT) or Stavudined4T) + Lamivudine(3TC)+ Nevirapine(NVP)*

*Pregnant women who initiate Nevirapine containing antiretroviral treatment when CD4> 250 cells have higher risk of Nevirapine related hepatotoxicitiy. This happens during first months of treatment but can occur at any time and can progress very rapidly. There are reports of pregnant women who died from liver failure attributed to NVP treatment. Hence it is recommended to carry out additional liver function tests (Bilirubin and transaminases).

Treating pregnant women with HAART suppresses the viral load and reduces mother to child HIV transmission.

b)ARV regimens in Children:

(Adapted from WHO Scaling up Antiretroviral Therapy in Resource-limited settings: Treatment Guidelines for a Public Health Approach)

The laboratory diagnosis of HIV infection in infants aged less than 18 months is difficult due to the persistence of maternal antibody. HIV DNA PCR is needs to established the diagnosis at this stage. WHO recommendations for the initiation of ARV therapy in children is related age. CD4 cell percentage is recommended for decision making on ARV treatment rather than absolute CD4 cell count, because absolute CD4 varies with age .

When to start ARV in children:

Age	HIV diagnosis	Treatment Recommendation
<18 months	Infant is HIV antibody positive(Note: must be confirmed at 18 months)	*WHO Pediatric Stages 2 and 3 with CD4<20%
<18 months	Positive virological test	Stage 3 irrespective of CD4% Stage 1 and 2 if CD4<15%
> 18 months	HIV antibody positive	Stage 3, irrespective CD4% Stage 1 and 2 if CD4<15%
If CD4 not available, start ARV if Stage 3		

* WHO Staging for HIV disease in children (Annex)

What to start:

HAART in children shows reduction in morbidity and mortality (ref,). Drug doses must be adjusted as a child grows to avoid under dosage and the development of resistance. Some ARVs available for adults are also available in formulations for children. Pediatric ARV dosages are given in Annex. ART should never be initiated without preparation of the child and family for the complex task of long-term therapy

Recommended first-line ARV regimen for children:

- ***For children < 3 years and weight < 10kgs***

Zidovudine (AZT) or Stavudine(d4T)

+

Lamivudine(3TC)

+

Nevirapine (NVP)

- ***For children > 3years and weight > 10kgs***

Zidovudine (AZT) or Stavudine(d4T)

+

Lamivudine (3TC)

+

Nevirapine(NVP)/Efavirenz(EFV)*

*(Efavirenz (EFV) cannot be used currently in children under 3 years of age because of a lack of appropriate formulation and dose information)

If mother has received ARV during pregnancy either to reduce MTCT or for her own disease, there is a possibility that the baby may become infected with drug-resistant virus .It is not known whether ARV choices should be modified for infants who have exposed to ARVs used for prevention of MTCT. Large studies are under way to study this. Until data available on this issue the same recommended regimen should be prescribed.

Recommended first line regimen when NNTI-based therapy is contraindicated:

Zidovudine (AZT)or Stavudine(d4T)

+

Lamivudine (3TC)

+

Nelfinavir (NLV) or Lopinavir/Ritonavir(LPV/r)*

* If available and requires cold chain

Monitoring Children on HAART:

Clinical assessment of infants and children receiving ARVs include:

Weight and height growth

Developmental milestones

Neurological symptoms

Frequency of infections (Bacterial infections, oral Thrush and. or other Opportunistic infections)

Laboratory monitoring of ARVs:

Investigations	Baseline	1st month	3rd month	6th month	Every 6 months
Complete blood count	X		X	X	X
Haemoglobin		X (if on AZT only)			
LFT(Serum Bilirubin,SGPT)	X	X (if on NVP only)	X	X	X
CD4% (< 6yrs) Absolute CD4 and CD4% (>6yrs)	X		X	X	X

Symptom directed investigations to diagnose Opportunistic infections and ARV toxicities should be done on follow-up.

Reasons for switching ARV in infants and children:

Definition of Treatment failure:

Clinical criteria:

- Lack of growth among children who show an initial response to treatment or decline in growth among children who show an initial growth response to therapy.
- Loss of neurodevelopmental milestones or development of encephalopathy
- Occurrence of new opportunistic infection or malignancy
- Recurrence of prior opportunistic infections.

CD4 criteria:

- Return of CD4 cell percentage (or for children > 6yrs, of absolute CD4 cell count) to pretreatment baseline or below in absence of other concurrent infection.
- >50% fall from peak level on therapy of CD4 percentage (or for children > 6yrs , of absolute CD4 cell count) in absence of concurrent infection

What to switch:

Recommended second-line ARV regimens for infants and children with treatment failure:

1st line ARVs		**2nd line ARVs**
Zidovudine (AZT)or Stavudine(d4T)	———	**Abacavir (ABC)**
+		+
Lamivudine (3TC)	———	**Didanosine(ddI)**
+		+
Nevirapine(NVP)/Efavirenz(EFV)	———	**Nelfinavir (NLV) or Lopinavir/Ritonavir(LPV/r)* or Saquinavir/Ritonavir(SQV/r) if weight>25kg**

* if available and requires cold chain

c) ARV regimens in HIV and Tuberculosis

Various studies in Asia show Tuberculosis is the most common opportunistic infection. (ref,ref). For many patients in the region TB is the presenting manifestation in HIV-infected persons. Several HIV-infected persons who are co infected with TB need ARVs. Rifampicin , a main stay anti-TB medication has drug interaction with protease inhibitors and the risk of liver toxicity is high when Nevirapine containing antiretroviral treatment is given to persons on Rifampicin containing TB treatment.(ref). Based on a published study from the region around 10% of the co-infected persons develop immune reconstitution syndrome when HAART is initiated along with anti-tuberculosis therapy. (ref). Simultaneous TB treatment and HAART has high pill burden which can result in poor drug adherence to both the diseases.

Due to these complex issues the following guidelines is recommended for HIV-TB infected individuals:

CD4 cell count	When to start HAART	Recommended regimen
CD4<200	Start ART as soon as TB treatment is tolerated(between 2 weeks and 2 months)	AZT or d4T+3TC+EFV*
CD4 200-350	Start ART after 2 months of TB treatment	AZT or d4T+3TC+EFV Or AZT or d4T+3TC+NVP in case of rifampicin-free continuation phase TB treatment regimen
CD4>350	Defer ART. Complete TB treatment and evaluate for ART initiation criteria	
CD4 not available	If the patient is in Stage 4, start ART after 2 weeks of TB treatment.	AZT or d4T+3TC+EFV*

*If EFV not available in the program then,NVP containing regimen can be used. Close monitoring for liver toxicities are recommended. Alternatives to EFV include LPV/r and ABC

d) ARV regimens in Injecting Drug users:

The criteria for initiating HAART in drug users are the same as the general recommendations. Although the treatment of HIV disease in this population is the same and can be successful, injection drug users with HIV disease present special treatment challenges. These include existence of co-morbid conditions, limited access to HIV care, inadequate adherence to HAART, medication side effects and toxicities, need for substance abuse treatment and the complexities of drug interactions. Common co-existing conditions seen in injecting drug users are tuberculosis, skin and soft tissue infections, recurrent bacterial pneumonia, endocarditis, hepatitis B and C, and neurologic and renal disease. Studies for the Asian region shows 70-80% of the injecting drug users are harboring Hepatitis C virus.(ref).

IDUs should be enrolled in substance de-addiction programs. Methadone, oral long acting opiate agonist, is the most successful treatment for opiate addiction. Its use is associated with decreased heroin use, improved quality of life and decreased needle sharing.

Methadone and NNRTIs have drug interactions. Nevirapine and efavirenz are potent inducers of p450 enzymes and have been associated with significant decreases in methadone levels.

Adherence to ARVs is a major issue in IDUs. Hence fixed dose combination pills and once daily regimens are preferred for IDUs. Directly observed therapy with counseling on life style modifications is recommended.

13. Adherence to ARVs:

Studies from the developed world shows more than 95% adherence to HAART is needed to achieve maximum benefit of HAART. (ref) Poor adherence to ARVs can lead to blips in viral load which can lead to the development of ARV resistance strains.

Reasons for poor adherence:

Travel/ being away from home

Changing schedules and routines

Competing priorities of day to day activities such as work and child care

Forgetfulness

Lack of family support

Secrecy and stigma and non disclosure to HIV diagnosis to spouse and family members

Cultural belief and fears about medication

Side effects

Number of pills and number of doses each day

Difficulty in swallowing the medications

Inadequate understanding of medication regimen

Lack of food

Lack of cool storage (if required)

Non-availability of drugs

High cost

How to improve adherence:

Never initiate HAART without proper counseling on ARVs.

Discuss with the patient that ARVs are life long and improves quality of life only if taken for prolonged period without interruption.

Involve DOT, family members and support groups to improve adherence.

Ensure uninterrupted supply of medications.

Provide pill box and pill count is advised while refilling to measure adherence.

14. Drug resistance:

Currently 10% of new infections in developed world involve HIV strains resistance to at least one drug. In a recently published study from India on the prevalence of ARV resistance strains in drug naïve patients shows 7% of the individuals had NRTI mutations and 11% had NNRTI mutations. (ref)

The most common reason for the development of ARV resistance is due to poor adherence to ARVs. ARV resistance can be measured by phenotypic and genotypic assays. These assays are expensive and needs sophisticated equipments and trained molecular virologists. Hence these assays are not recommended for initiating or switching therapy in this guideline. When these assays become widely available the relevant guidelines will be updated for use.

WHO has recently developed a global HIV drug resistance surveillance program (Resnet) to monitor the pattern and prevalence of ARV drug resistance globally.(ref)

15. Post exposure prophylaxis (PEP)

Universal precautions should be strictly adopted while handling blood and other body secretions. The chance HIV transmission following mucocutaneous exposure is 0.09% and through percutaneous exposure is 0.3% (ref).

In case of an accidental exposure, the following procedures should be adopted:

- The injured/exposed site should wash immediately with running water.
- Never squeeze the exposed area nor apply any caustic agent.
- PEP should be initiated within 36 hrs, preferably within 2 hrs.

Exposure	HIV status of source		
	HIV+ low risk*	HIV+ high risk**	Unknown HIV status
Percutaneous			
Not severe	2 drugs	3 drugs	Consider 2 drugs
Severe	3 drugs	3 drugs	Consider 2 drugs
Mucocutaneous			
Small volume	Consider 2 drugs	2 drugs	Consider 2 drugs
Large volume	2 drugs	3 drugs	Consider 2 drugs

* Low risk- Asymptomatic

** High risk- Stage 2, 3 or 4

2 drugs: AZT/d4T+3TC

3 drugs: AZT/d4T+3TC+ IDV/r or LPV/r or SQV/r.

Nevirapine and Abacavir should never be used as PEP drug. If the source patient is on ARVs, then an HIV expert should be consulted to make the choice of PEP drugs since the source might harbour a resistance virus.

PEP drugs should be continued for 4 weeks.

Exposed HCW s should not donate blood and breast feed children till HIV infection is ruled out.

Serology: Obtain at baseline, 6 weeks, 3 months and 6 months. Do not use HIV PCR for diagnosis in following PEP.

All accidental exposures should be reported to the supervisor.

16. Prevention of Mother to Child HIV transmission:

Risk factors for Mother to Child Transmission of HIV

Maternal factors

- High HIV RNA level in the blood
- Advanced HIV disease

Obstetrical factors

- Vaginal delivery
- Rupture of membranes longer than 4 hrs

Infant factors

- Prematurity < 37 weeks

Breast feeding

- Advanced maternal disease
- Longer duration of breast feeding

How to prevent MTCT:

If the pregnant women have indications to start HAART as described in chapter 12(a), HAART should be started. (Chapter 12-a) HAART can suppress the viral load to the maximum and can lead to reduction in MTCT.

If the pregnant woman doesn't satisfy criteria to start HAART, then ARV prophylaxis should be initiated.

AZT 300 mg bid should be initiated any time after 14 weeks till delivery to the mother. C-section is recommended.

Avoid breast feeding. Pros and cons about breast feeding should be discussed with the mother. Efforts should be made to provide infant formula feed. Counseling on safe water to prepare formula feed should be done.

Baby should receive Syrup. AZT 4 mgs/kg PO 12 hourly for 6 weeks.

If the mother present to the clinic in labor, then *single dose Nevirapine (200 mgs) should be given PO on the onset of labor. Infant should receive single dose Nevirapine 2 mgs/kg PO within 72hrs after birth.

* Recent reports show that women who have received single dose NVP as ARV prophylaxis for MTCT intervention, there could be a potential danger for those women to develop resistance to NVP and hence NNRTI cannot be used in those women when they need HAART.(Eshelman et al.ref) . These issues are under further study.

17) Conclusions:

Appendices

Appendix A: Dosages of antiretroviral drugs for adults and adolescents

Appendix B: WHO staging of HIV disease in adults and adolescents

Appendix C: Drug interaction between ARVs and commonly used medications.

Appendix D: Human immunodeficiency virus paediatric immune category classification system based on age-specific CD4+T cell count and percentage

Appendix E: Dosages of Paediatric formulations

Appendix F: WHO staging system for HIV disease in Children

Appendix G: Diagnosis and Mangement of common Opportunistic Infections

Appendix H: Prophylaxis fore opportunistic infections

References