

Screening of children for HIV status

In newborns and in children, the following groups need to be tested:

- babies of HIV positive mothers
- abandoned babies / street children
- babies of mothers with high risk behaviour (e.g. drug addicts / prostitutes / multiple sex partners / single-teenage or underage)
- sexually abused children and children with sexually transmitted disease
- children receiving regular blood transfusions or blood products e.g. Thalasseemics

Deliveries and infant nursing

- standard precautions must be observed at all times. It is vital to use protective barriers such as arm length gloves, mask, goggles and gown with waterproof sleeves. Boots are to be used for institutional deliveries:
 - during deliveries.
 - during handling of placenta tissue
 - during handling of babies such as wiping liquor off babies
 - all equipment, including resuscitation equipment should be cleaned and sterilised
- for home deliveries, battery operated suction device should be used
- standard precautions are to be observed in caring for the babies
- for parents or relatives, gloves are given for use when handling the placenta after discharge, or during burial of stillbirth or dead babies at home. The placenta from HIV positive mothers should be soaked in formalin solution before disposal. Alternatively, the placenta can be sealed in a plastic bag or other leakproof container with clear instructions to parents not to remove it from the container.

Immunisation

- vaccines protect HIV-infected children from getting severe vaccine-preventable diseases, and generally well tolerated.
- all routine vaccinations can be given according to schedule, with special precautions for live vaccines i.e. BCG, OPV and MMR:
 - BCG: safe in child is asymptomatic and not immunosuppressed (e.g. at birth); omit if symptomatic or immunosuppressed
 - OPV: safe; small theoretical risk of transmission to other immunocompromised family members. Preferably give IPV (killed polio vaccine) if available.
 - MMR: safe; omit in children with severe immunosuppression (CD4<15%)
- other recommended vaccines:
 - pneumococcal polysaccharide vaccine when > 2 years of age; booster 3-5 years later. Where available, use Pneumococcal conjugate vaccine (more immunogenic)
 - varicella-zoster vaccine, where available. 2 doses with 2 months interval. omit in those with severe immunosuppression (CD4 < 15%)

Despite vaccination, remember that long term protection may not be achieved in severe immune suppression i.e. they may still be at risk of acquiring the infections!

Interventions to limit perinatal transmission

Vertical transmission of HIV may occur while in utero, during the birth process or through breast-feeding. The rates vary from 25 - 30%.

Breastfeeding confers an additional 14% risk of transmission, and is therefore contraindicated.

The risk of transmission of HIV infection from blood transfusion is very small, though not absent, and thus blood and blood products should be used judiciously.

Several interventions have proven effective in reducing vertical transmission:

- total substitution of breastfeeding with infant formula
- elective Caesarean section
- antiretroviral (ARV) prophylaxis

Management of Babies Born to HIV Infected Mothers

Children born to HIV positive mothers are usually asymptomatic at birth. However, all will have acquired maternal antibodies. In uninfected children, antibody testing becomes negative by 10 - 18 months age.

During pregnancy

- counsel mother regarding:
 - transmission rate (without intervention) –25 to 30%
 - ARV prophylaxis reduces transmission to 8%
 - elective LSCS + ARV prophylaxis reduces transmission to ~ 3%
- to feed with infant formula as breast feeding doubles the risk of transmission
- difficulty in making early diagnosis because of presence of maternal antibody in babies. Stress importance of regular blood tests and follow-up.

Neonatal period

- admit to ward or early review by paediatric team (if not admitted).
- examine baby for
 - evidence of other congenital infections
 - symptoms of drug withdrawal (reviewing maternal history would be helpful)
- most babies are asymptomatic and only require routine perinatal care
- start on prophylaxis ARV as soon as possible (see Figure 1)
- sample blood for:
 - HIV DNA PCR (done in IMR, do not use cord blood; sensitivity 90% by 1 month age)
 - FBC
 - Other tests as indicated:
 - LFT, RFT, HbsAg, Hepatitis C, Toxoplasmosis, CMV, VDRL serology

Table 1. Factors associated with higher transmission rate

Maternal

- low CD 4 counts
- high viral load
- advanced disease
- seroconversion during pregnancy

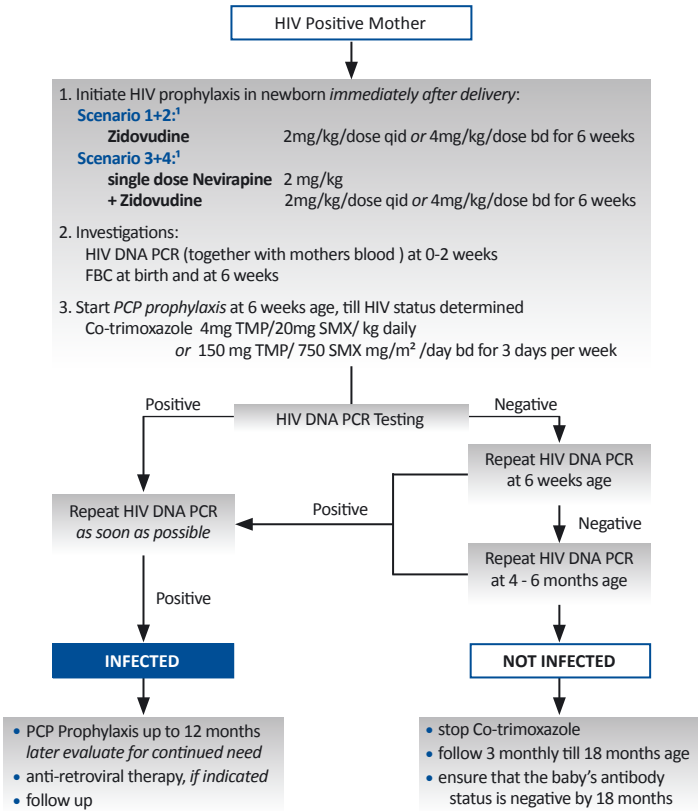
Foetal

- premature delivery of the baby

Delivery and procedures

- invasive procedures such as episiotomy
- foetal scalp electrodes
- foetal blood sampling and amniocentesis
- vaginal delivery
- rupture of membranes > 4 hours
- chorioamnionitis

Figure 1. Management of HIV exposed infants (from Malaysian CPG Guidelines 2008)



¹ foot note:

Scenario 1: HIV - infected mother who is already on HAART

Scenario 2: HIV - infected mother who has been started on Zidovudine at 14-28 weeks gestation

Scenario 3: HIV - infected mother at delivery who has received inadequate ARV (< 4 weeks)

Scenario 4: Infant born to HIV - infected mother who has not received any ARV

Abbreviations:

ARV, antiretroviral prophylaxis; HAART, highly active antiretroviral therapy;

PCP, pneumocystis carinii pneumonia.

Management of HIV in Children

Clinical Features

Common presenting features are:

- persistent lymphadenopathy
- failure to thrive
- recurrent infections (respiratory, skin, gastrointestinal)
- hepatosplenomegaly
- developmental delay, regression

Diagnosis of HIV infection

- in children > 18 months age: 2 consecutive positive HIV antibody tests.
- in children < 18 months age: 2 positive HIV DNA PCR tests.

Monitoring

- monitor disease progression through clinical, immunological (CD4+ count or %) and viral load status. Viral load assay is available in regional centres.
- CD4+ count and viral load assay are done at diagnosis, 2-3 months after initiation or change of ART and every 3-4 months thereafter (more frequently if change of therapy is made or progression of disease occurs).

Antiretroviral Therapy

Clinical outcome following the use of highly active antiretroviral therapy (HAART) in children is excellent, with reduced mortality (67 - 80%) reported from various cohorts. However, this needs to be balanced with: failure of current drugs to eradicate infection, medication side effects and compliance-adherence issues.

When to start?

- before starting ART, intensive education to parents, care-givers and older children-patients need to be stressed. Do not start in haste as we may repent at leisure! Assess family's capacity to comply with often difficult and rigid regimens. Stress that non-adherence to medications allows continuous viral replication and encourages the emergence of drug resistance and subsequent treatment failure.
- young infants have a much higher risk of disease progression to clinical AIDS or death when compared to older children or adults and hence the treatment recommendations are more aggressive. Recommendation for when to start ARV is shown in Table 6.
- please consult a specialist/consultant before starting treatment.

Table 2. Goals of therapy

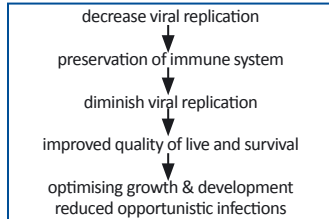


Table 3. WHO classification of HIV-associated immunodeficiency using CD4 count

Classification of HIV-associated Immunodeficiency	Age-related CD4 values			
	<11 months (CD4 %)	12-35 months (CD4 %)	36-59 months (CD4 %)	≥5 years (cells/mm ³ or CD4 %)
Not significant	>35	>30	>25	>500
Mild	30-35	25-30	20-25	350-499
Advanced	25-29	20-24	15-19	200-349
Severe	<25	<20	<15	<200 or <15%

Clinical categories

There are 2 widely used clinical classification systems: CDC's 1994 Revised Paediatric Classification and the WHO Clinical Classification system. Both classification systems are similar with only minor differences

Table 4. WHO Clinical Staging Of HIV for Infants and Children With Established HIV infection (Adapted from WHO 2006)

<p>Clinical Stage 1 (Asymptomatic) asymptomatic persistent generalized lymphadenopathy</p> <p>Clinical stage 2 (Mild) * unexplained persistent hepatosplenomegaly papular pruritic eruptions extensive wart virus infection extensive molluscum contagiosum recurrent oral ulcerations unexplained persistent parotid enlargement lineal gingival erythema herpes zoster recurrent or chronic upper respiratory tract infections (otitis media, otorrhoea, sinusitis, tonsillitis) fungal nail infections</p> <p>Clinical stage 3 (Advanced) * unexplained moderate malnutrition not adequately responding to standard therapy unexplained persistent diarrhoea (> 14 days) unexplained persistent fever (above 37.5 °C, intermittent or constant, > 1 month) persistent oral candidiasis (> 6 weeks of life) oral hairy leukoplakia acute necrotizing ulcerative gingivitis, periodontitis lymph node TB pulmonary TB severe recurrent bacterial pneumonia symptomatic lymphoid interstitial pneumonitis chronic HIV-associated lung disease including bronchiectasis unexplained anaemia (<8.0 g/dl), neutropenia (<0.5 x 10⁹/L) or chronic thrombocytopenia (<50 x 10⁹/L)</p>	<p>Clinical stage 4 (Severe) * unexplained severe wasting, stunting or severe malnutrition not responding to standard therapy pneumocystis pneumonia recurrent severe bacterial infections (e.g. empyema, pyomyositis, bone or joint infection, meningitis, but excluding pneumonia) chronic herpes simplex infection (orolabial or cutaneous of > 1 month's duration, or visceral at any site) extra pulmonary TB Kaposi sarcoma oesophageal candidiasis (or Candida of trachea, bronchi or lungs) central nervous system toxoplasmosis (after the neonatal period) HIV encephalopathy cytomegalovirus (CMV) infection; retinitis or CMV infection affecting another organ, onset age > 1 month extra pulmonary cryptococcosis (including meningitis) disseminated endemic mycosis (extra pulmonary histoplasmosis, coccidiomycosis) chronic cryptosporidiosis (with diarrhoea) chronic isosporiasis disseminated non-tuberculous mycobacteria infection cerebral or B cell non-Hodgkin lymphoma progressive multifocal leukoencephalopathy HIV-associated cardiomyopathy or nephropathy</p> <p><i>footnote: (*) Unexplained refers to where the condition is not explained by other causes.</i></p>
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Table 5. Main categories of antiretroviral drugs available in Malaysia

Nucleoside reverse transcriptase inhibitors (NRTI)	Non nucleoside reverse transcriptase inhibitor (NNRTI)	Protease inhibitors (PI)
Zidovudine (ZDV)	Nevirapine (NVP)	Ritonavir
Stavudine(d4T)	Efavirenz (EFZ)	Indinavir
Lamivudine (3TC)		Lopinavir/Ritonavir (Kaletra)
Didanosine (ddl)		Saquinavir
Abacavir (Abc)		
Fixed-dose combination tablets (FDC)		
ZDV + 3TC combined tablet (Combivir / Duovir)		
d4T+ 3TC + NVP combined tablet (SLN 30 / 40)		

Which drugs to use?

Always use combination of at least 3 drugs (see Table 7):

- either
 - 2 NRTI* + 1 NNRTI (Efavirenz (age > 3 years) or Nevirapine (age < 3 years))
 - or
 - 2 NRTI* + 1 PI (Lopinavir/r)

* Recommended 2 NRTI combinations: ZDV + 3TC; ZDV + ddI; ddI + 3TC

Alternative 2 NRTI combinations : d4T + 3TC ; d4T + ddI (use of d4T-based regimen is associated with higher incidence of lipodystrophy)

- Not Recommended
 - any monotherapy (except mother-to-child transmission prophylaxis during neonatal period)
 - d4T + ZDV: pharmacologic and antiviral antagonism

Table 6. When to start ARV? (adapted from Malaysian CPG 2008)

Age	Initiate Treatment	Consider	Defer
<12 months	symptomatic (WHO Stage 2,3,4) OR asymptomatic (WHO Stage 1) and CD4 < 25%	asymptomatic (WHO Stage 1) and CD4 ≥25%	-
1-<3 years	AIDS or significant HIV-related symptoms (WHO Stage 3* or 4) OR asymptomatic, mild symptoms (WHO Stage 1, 2) and CD4 < 20%	asymptomatic or mild symptoms and - CD4 20-24 % or - VL ≥ 100,000 copies /ml	asymptomatic and - CD4 ≥ 25 % and - VL <100,000 copies /ml
3-12 years	AIDS or significant HIV-related symptoms (WHO Stage 3* or 4) OR asymptomatic, mild symptoms (WHO Stage 1, 2) and CD4 < 15%	asymptomatic or mild symptoms and - CD4 15-24 % or - VL ≥100,000 copies /ml	asymptomatic and - CD4 ≥ 25 % and - VL <100,000 copies /ml
>12 years	AIDS or significant HIV-related symptoms (WHO Stage 3* or 4) OR asymptomatic, mild symptoms (WHO Stage 1 & 2) and CD4 < 200 cells /mm ³ or <15%	asymptomatic or mild symptoms and - CD4 201-350 cells/mm ³ or - VL ≥100,000 copies /ml	asymptomatic and - CD4 >350 cells/mm ³ and - VL <100,000 copies /ml

* Except with Tuberculosis, lymphoid interstitial pneumonitis (LIP), Oral hairy leukoplakia (OHL) or thrombocytopenia (Starting antiretroviral in children with these conditions will depend on their CD4 count / % VL, Viral Load

When to change?

- treatment failure based on clinical, virologic and immunological parameters e.g. deterioration of condition or dropping of CD4 count/%.
- toxicity or intolerance of the current regimen

If due to toxicity or intolerance:

- choose drugs with toxicity profiles different from the current regimen
- changing a single drug is permissible
- avoid reducing dose below lower end of therapeutic range for that drug

If due to treatment failure:

- assess and review adherence
- preferable to change all ARV (or at least 2) to drugs that the patient has not been exposed to before.
Choices are very limited! Do not add a drug to a failing regime.
- consider potential drug interactions with other medications
- when changing therapy because of disease progression in a patient with advanced disease, the patient's quality of life must be considered.
- doing genotypic resistant testing will help to choose the appropriate ARV, however, the test is not widely available in Malaysia
- consult infectious diseases specialist before switching.

Table 7. Antiretroviral drugs dosages and common side effects

Drug	Dosage	Side effects	Comments
Zidovudine (AZT)	180-240mg/m ² /dose bd Neonate: 2mg/kg qid or 4mg/kg bd (max. dose 300mg bd)	anaemia, neutropenia, headache	large volume of syrup not well tolerated in older children
Didanosine (ddI)	90-120mg/m ² /dose bd (max. dose 200mg bd)	diarrhoea, abdo pain, peripheral neuropathy	taken on empty stomach (1hr before or 2h after food)
Lamivudine (3TC)	4mg/kg/dose bd (max. dose 150mg bd)	diarrhoea, abdo pain; pancreatitis (rare)	well tolerated; use solution within 1 month of opening
Stavudine (d4T)	1mg/kg/dose bd (max. dose 40mg bd)	headache, peripheral neuropathy, pancreatitis	capsule may be opened and sprinkle on food or drinks
Abacavir (Abc)	8 mg/kg/dose bd (max. dose 300 mg bd)	diarrhoea, nausea, rash, headache; hypersensitivity, Steven-Johnson (rare)	NEVER restart Abc after hypersensitivity reaction (may cause death)
Efavirenz (EFZ)	350mg/m ² od 13-15kg 200mg 15-20kg 250mg 20-25kg 300mg 25-32kg 350mg 33-40kg 400mg > 40kg 600mg od	rash, headache, insomnia	Inducer of CYP3A4 hepatic enzyme; so has many drug interactions Capsules may be opened and added to food
Nevirapine (NVP)	150-200mg/m ² /day od for 14 days, then increase to 300-400mg/m ² /day bd (max. dose 200mg bd)	severe skin rash, headache, diarrhea, nausea	little data on use with PI. Practice is to increase PI dose by about 30%
Ritonavir (RTV)	350-450mg/m ² /dose bd (max. dose 600mg bd)	vomiting, nausea, headache, diarrhoea, hepatitis (rare)	take with food to increase absorption and reduce GI side effects; Solution bitter as contains 43% alcohol
Kaletra (Lopinavir/ Ritonavir)	230/57.5mg/m ² /dose bd 7-14kg 12/3 mg/kg bd 15-40kg 10/2.5mg/kg bd > 40kg 400/100mg bd	diarrhea, asthenia	low volume, but a bitter taste. Higher dose used with NNRTI
Indinavir (IDV)	500mg/m ² /dose, tds (max. dose 800mg tds)	headache, nausea, abdominal pain, hyperbilirubinemia, renal stones	use in older children that can swallow tablets; Take on an empty stomach. Advise to drink more fluids

Follow up

- usually every 3 - 4 months, if just commencing/switching HAART, then every 2 weeks
- ask about medication:
 - adherence (who, what, how and when of taking medications)
 - side effects e.g. vomiting, abdominal pain, jaundice
- examine: growth, head circumference, pallor, jaundice, oral thrush, lipodystrophy syndrome (if on Stavudine &/or PI)
- FBC, CD4 count, viral load 3-4 monthly, RFT, LFT, Ca/Po₄ (amylase if on ddl) 6 monthly;
- if on PI also do fasting lipid profiles and blood sugar yearly
- explore social, psychological, financial issues e.g. school, home environment. Many children are orphans, live with relatives, adopted or under NGO's care. Referral to social welfare often required. Compliance - adherence to therapy strongly linked to these issues.

Other issues

- HIV / AIDS is a notifiable disease. Notify health office within 1 week of diagnosis.
- screen other family members for HIV.
- refer parents to Physician Clinic if they are HIV infected and not on follow up.
- disclosure of diagnosis to the child (would-be teenager, issues on sexual rights)
- be aware of Immune Reconstitution Inflammatory Syndrome (IRIS)
 - in this condition there is a paradoxical worsening of a known condition (e.g. pulmonary TB or lymphadenitis) or the appearance of a new condition after initiating ARV. This is due to restored immunity to specific infectious or non-infectious antigens.

Horizontal transmission within families

Despite sharing of household utensils, linen, clothes, personal hygiene products; and daily interactions e.g. biting, kissing and other close contact, repeated studies have failed to show transmission through contact with saliva, sweat, tears and urine (except with exposure to well defined body fluids i.e. blood, semen, vaginal fluids).

It is important to stress that the following has not transmitted infection:

- casual contact with an infected person
- swimming pools
- droplets coughed or sneezed into the air
- toilet seats
- sharing of utensils such as cups and plates
- insects

Note: It is difficult to isolate the virus from urine and saliva of seropositive children. So day care settings are not a risk. However, due to a theoretical risk of direct inoculation by biting, aggressive children should not be sent to day care. Teachers should be taught to handle cuts/grazes with care.

Guidelines for post exposure prophylaxis

Goal is to prevent HIV infection among those sustaining exposure, and provide information and support during the follow up until infection is diagnosed or excluded with certainty

Risk for occupational transmission of HIV to Health Care Workers (HCW)

- risk for HIV transmission after a percutaneous exposure to HIV infected blood is 0.3%; risk after mucous membrane exposure is 0.1%.
- risk is dependent on :
 - type, volume of body fluid involved
 - type of exposure that has occurred
 - viral load of the source patient
 - disease stage

Treatment of an Exposure Site

- wash wounds, skin exposure sites with soap, water; flush mucous membranes with water
- notify supervisor; refer HCW to designated doctor as in hospital needlestick injury protocol