

This Guideline is intended a guide for clinical practice, based on the best available evidence at the time of development. Adherence to this guideline may not necessarily guarantee the best outcome in every case. Every health care provider is responsible for the management of his/her unique patient based on the clinical picture presented by the patient and the management options available locally.

Review of the Guidelines

This guideline was issued in 2008 and will be reviewed in 2012 or sooner if new evidence becomes available

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GUIDELINE DEVELOPMENT AND OBJECTIVE

GUIDELINE DEVELOPMENT

The development group for this guideline comprised of paediatricians, a family medicine specialist, a medical microbiologist and pharmacist, from the Ministry of Health and the Ministry of Higher Education, Malaysia. During the process of development of this guideline, there was active involvement of a review committee which consisted of paediatricians from the public and private sector together with a public health specialist and a clinical virologist.

This document is the first Clinical Practice Guideline (CPG) on the Management of HIV infection in Children and Adolescents for Malaysia, updating the 2nd Consensus Guideline (2001) and has been developed in parallel with the CPG on Management of HIV Infection in Pregnancy.

Literature search was carried out at the following electronic databases, International Health Technology Assessment Websites, PUBMED, Cochrane Database of Systemic Reviews (CDSR) Journal full text via the OVID search engine, Comprehensive; Database of Abstracts of Reviews of Effectiveness; Cochrane Controlled Trials Registered, Clinical Trial Registry and EBSCO search engine. MEDLINE search was limited to children "all child" (0-18 years). References from relevant articles retrieved were searched to identify further studies. The following free text terms or MeSH term were used either singly or in combination: "HIV infection, mother-to-child-transmission, perinatal HIV infection, antiretroviral therapy, side effects, co-infections, tuberculosis, toxoplasmosis, syphilis, hepatitis B infection, hepatitis C infection, cytomegalovirus infection, human immunodeficiency virus, diagnosis, HIV DNA PCR, HIV RNA assays, infants, breastfeeding, infant feeding, HIV prophylaxis AND cotrimoxazole, HIV prophylaxis AND pneumocystis, AIDS-Related Opportunistic Infections AND Trimethoprim-Sulfamethoxazole; combination, "immunisation" "vaccination" and BCG, hepatitis B, diphtheria, pertussis, tetanus, polio (oral and injectable), Haemophilus influenzae type B, measles, mumps, rubella, meningococcal, pneumococcal and varicella; antiretroviral, HAART, therapy, initiate, start, commence, "begin" (in various combinations), HIV AND cardiac ; HIV AND neurology; HIV AND lung; HIV AND renal; HIV AND oncology; HIV transmitted resistance', 'primary resistance', 'HIV treatment naïve', "plasma decay HIV", "HIV immunologic response", "virologic response", "HIV treatment response", "monitoring", 'adherence', and 'immune reconstitution syndrome'.

Reference was also made to other guidelines on management which included the Public Health Service Task Force Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States (November 2, 2007), US Department of Health & Human Services

Guidelines for the Use of Antiretroviral Agents in HIV-1 Infected Adults & Adolescents (October 2006), American Academy of Pediatrics and Canadian Pediatric Society Guideline on the evaluation and treatment of the human immunodeficiency virus -1 -exposed infant (2004), National Institutes of Health Guidelines for the use of Antiretroviral Agents in Pediatric HIV infection (2006 & 2008), Royal College of Obstetricians & Gynaecologists Guideline On Management Of HIV In Pregnancy (2004), Guideline by the Canadian HIV Trials Network Working Group on Vertical HIV Transmission (2003) and WHO Guidelines Antiretroviral Therapy Of HIV Infection In Infants And Children In Resource Limited Settings: Towards Universal Access (2006), British HIV Association (BHIVA) Guidelines 2005, WHO Guidelines For HIV Drug Resistance Surveillance In Newly Diagnosed And Treatment-Naïve HIV Infected Subjects (2003). This guideline is based largely on the findings of systematic reviews and meta-analyses in the literature.

The evidence in the articles were graded using the modified version of those used by the Catalonia Agency for Health Technology Assessment and Research (CAHTAR) Spain, while the grading of recommendations in these guidelines was modified from the Scottish Intercollegiate Guidelines Network (SIGN). (Refer to inside back cover).

The clinical questions were divided into major subgroups and members of the development group were assigned individual topics within these subgroups. The group members met a total of twenty three times throughout the development of the guideline. All literature retrieved were appraised by individual members and presented in the form of evidence tables and discussed during group meetings. All statements and recommendations formulated were agreed by both the development group and review committees. Where the evidence was insufficient the recommendations were derived by consensus of the development group and review committees.

The draft guideline was posted on both the Ministry of Health Malaysia and Academy of Medicine, Malaysia websites for comment and feedback. This guideline has also been presented to the Technical Advisory Committee for Clinical Practice Guidelines, and the Health Technology Assessment and Clinical Practice Guidelines Council, Ministry of Health Malaysia for review and approval.

OBJECTIVE

The aim of the guideline is to assist clinicians in making evidence based decisions regarding:

1. Management of newborns with perinatal exposure to HIV infection
2. Appropriate management and treatment of HIV infection in infants, children and adolescents.

CLINICAL QUESTIONS

- What are the appropriate management strategies for the perinatally exposed newborn?
- What are the diagnostic tests available for the detection of HIV infection in infants and children?
- What are the appropriate treatment strategies for HIV infection in infants, children and adolescents?
- What are the complications associated with HIV infection and opportunistic infections in children infected with HIV and the management of these complications?
- What are the issues regarding disclosure of HIV infection in children and what are the possible approaches?

TARGET POPULATION

This guideline is developed for the management of HIV infection in perinatally exposed infants and infected children and adolescents (i.e. all individuals aged 0-18 years).

TARGET USER

This guideline is applicable to all primary care providers, family medicine specialists, paediatricians, physicians and other healthcare professionals who are involved in the management of HIV infection in children and adolescents aged 0 to 18 years.

EXCLUSION

This guideline does not address in detail issues of prevention, counselling, HIV and the looked-after child, nutritional aspects, palliative and terminal care in children with HIV infection.

CLINICAL INDICATORS FOR QUALITY MANAGEMENT

Indicator	Standard
Perinatal transmission of HIV-1 infection	<2%
Percent of perinatally exposed infants receiving ZDV within 24hrs of birth	100%
Percent of patients for whom a CD4 test (absolute and percentage) performed every 3-4 months	75%

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The draft guideline was reviewed by a panel of independent expert referees, who were asked to comment primarily on the comprehensiveness and accuracy of interpretation of the evidence supporting the recommendations in the guideline.

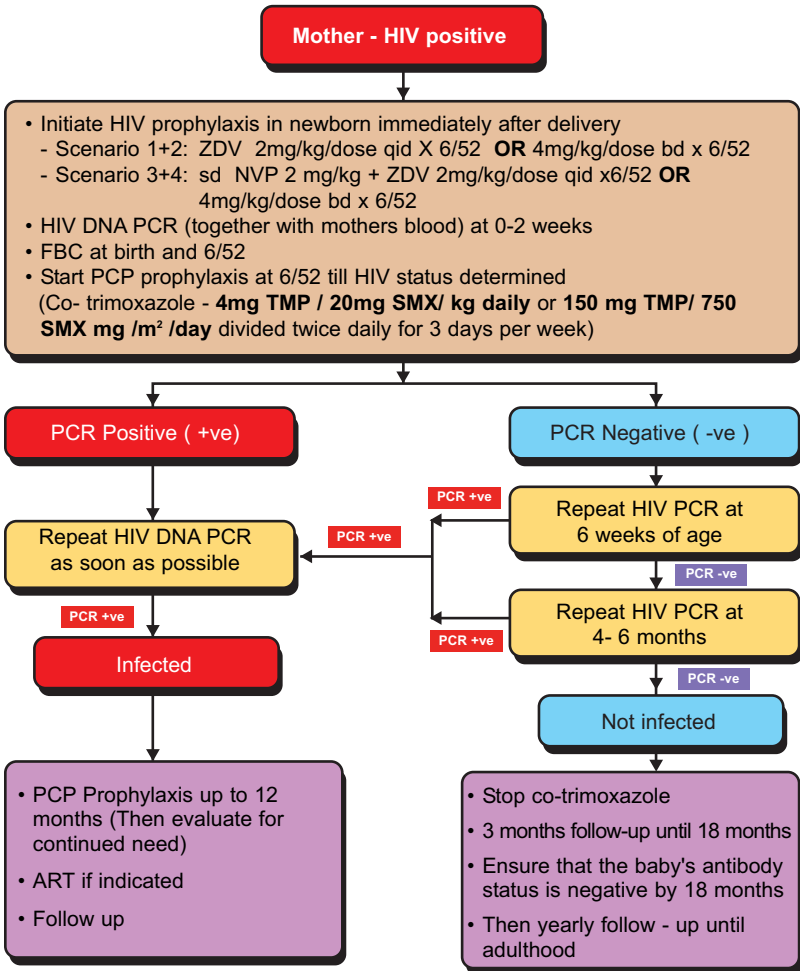
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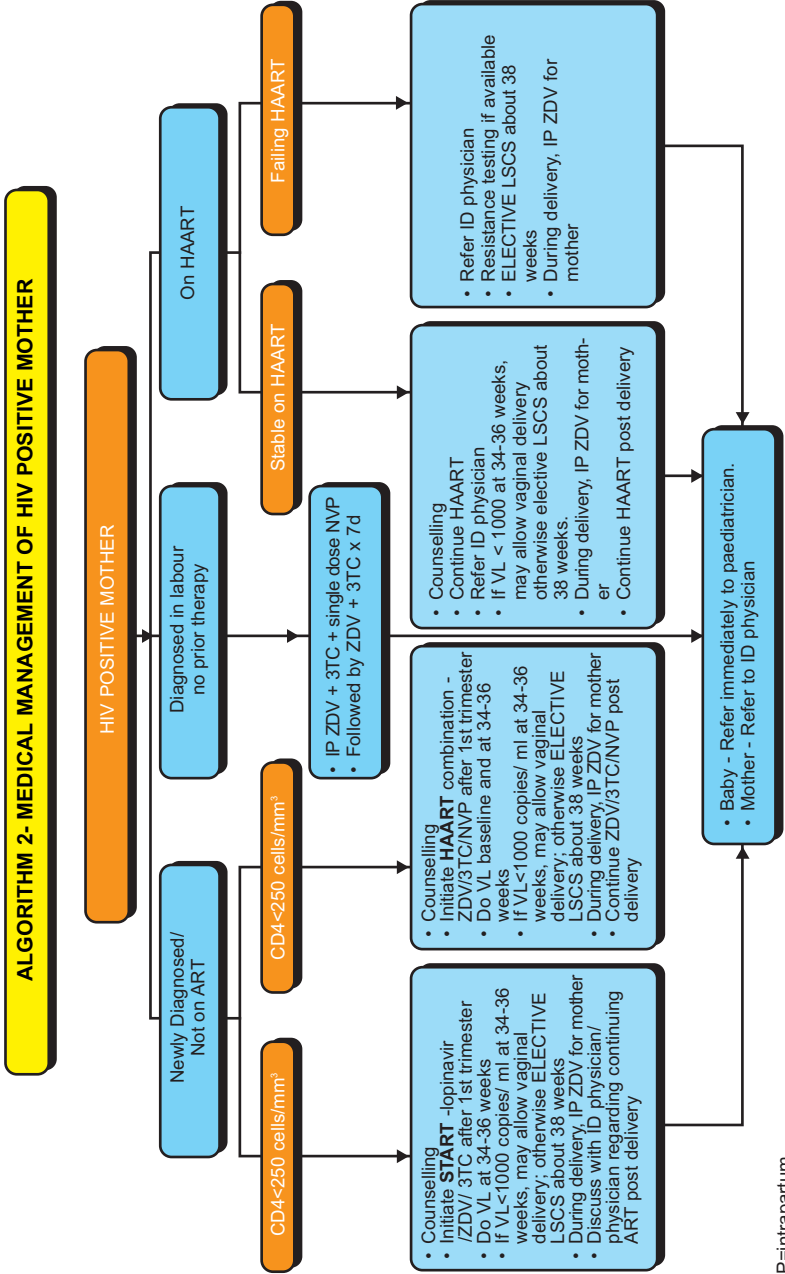
ALGORITHM 1-MANAGEMENT OF HIV EXPOSED INFANTS



Foot note:

- Scenario 1- HIV- infected pregnant mother who is already on HAART
- Scenario 2- HIV- infected pregnant mother who has been started on ZDV (between 14-28 weeks)
- Scenario 3- HIV- infected pregnant mother at delivery who has not received adequate ART (less than 4 weeks)
- Scenario 4 - Infant born to HIV -infected mother who has not received any ART

* For babies found abandoned at birth, the algorithm above is applied according to the rapid HIV test result while awaiting confirmation



IP=intrapartum

TABLE OF CONTENTS

GUIDELINE DEVELOPMENT AND OBJECTIVE	i
GUIDELINE DEVELOPMENT GROUP	
REVIEW COMMITTEE	vi
EXTERNAL REVIEWERS	vii
ALGORITHM 1: MANAGEMENT OF HIV EXPOSED INFANT	viii
ALGORITHM 2: MEDICAL MANAGEMENT OF HIV POSITIVE MOTHER	ix
	vii
1 INTRODUCTION	1
2. MANAGEMENT OF THE PERINATALLY EXPOSED INFANT	2
2.1 HIV PROPHYLAXIS	2
2.2 EVALUATION & CARE AT BIRTH	6
2.3 INVESTIGATIONS AT BIRTH	7
2.4 ADVICE AND COUNSELLING	9
2.5 FEEDING	10
2.6 IMMUNISATION	11
2.7 CLINICAL AND LABORATORY MONITORING OF THE PERINATALLY EXPOSED INFANT	16
2.8 PRIMARY PNEUMOCYSTIS JIROVECI PNEUMONIA PROPHYLAXIS FOR THE TREATMENT PERINATALLY EXPOSED INFANT	18
3. MANAGEMENT OF HIV INFECTED INFANTS, CHILDREN AND ADOLESCENT	21
3.1 MONITORING DISEASE PROGRESSION	21
3.2 ANTIRETROVIRAL THERAPY	21
3.2.1 Effectiveness of HAART	
3.2.2 When to initiate therapy	
3.2.3 Issues and choice for initial antiretroviral therapy	
3.2.4 Special Issues For Adolescents	
3.2.5 Treatment failure	
3.2.6. Management of medication toxicity or intolerance	
3.2.7 Short- term therapy interruption	
4. COMMON OPPORTUNISTIC INFECTIONS (OI) AND COMPLICATIONS IN HIV INFECTED CHILDREN	45
4.1 PATTERN OF OPPORTUNISTIC INFECTIONS	45
4.2 PREVENTING OPPORTUNISTIC INFECTIONS	45
4.2.1 Dosage and regimens for OI prophylaxis	
4.2.2 Safety of PCP prophylaxis medications	

5. NON INFECTIOUS COMPLICATIONS OF HIV	47
5.1 MALIGNANCY	47
5.2 NEUROLOGIC COMPLICATIONS	47
5.3 HIV-ASSOCIATED NEPHROPAHY	48
5.4 CARDIAC COMPLICATIONS	48
5.5 LYMPHOCYTIC INTERSTITIAL PNEUMONITIS (LIP)	48
6. OTHER ISSUES	
6.1 DISCLOSURE	48
6.2 AGE APPROPRIATE EDUCATIONAL & LIFESYLE ADVICE FOR CHILDREN AND ADOLESCENTS	51
REFERENCES	53-69
APPENDIX 1 - WHO clinical staging of HIV/AIDS for children with confirmed HIV infection	70
APPENDIX 2 - WHO clinical staging /AIDS for adults and adolescents with confirmed HIV infection	71
APPENDIX 3 - Immunological Classification	72
APPENDIX 4 - Antiretroviral Drugs	73-79
APPENDIX 5 - Tanner staging in adolescents	80
APPENDIX 6 - Investigations for opportunistic infections	82
APPENDIX 7 - Treatment for opportunistic infections	83-84
APPENDIX 8 - List of HIV Drugs Available in Malaysia	85
APPENDIX 9 - Additional Resources	86
LIST OF ABBREVIATIONS	87
ACKNOWLEDGEMENTS	88
DICLOSURE STATEMENT	88
SOURCES OF FUNDING	88
LEVEL OF EVIDENCE & GRADE OF RECOMMENDATION	

1. INTRODUCTION

By the end of 2006 there were estimated 2.3 million children globally below 15 years of age living with HIV with an estimated half a million new infections occurring in children for the year 2006.¹ In addition, of the estimated 10 000 new infections that occurred daily worldwide among adults in 2006, 50% were among women.

In Malaysia, the cumulative number of reported cases of HIV infection at end 2006 was 76 389 with 5830 reported cases for 2006. While women constituted only 1.16% of total new cases for 1990, this increased to 15.0% for 2006.

Children below of age 12 years of age constituted 1.5% of total reported cases for 2006, those aged 13-19 years 1.0% and those aged 20-29 years 2.7%.²

The vast majority of paediatric HIV infections are acquired vertically. Estimates from studies of prevention of mother-to-child transmission (PMTCT) suggest that in non-breastfeeding populations, about 50% of all HIV infections occur in the days before delivery and during labour and another third occur during late labour and actual passage through the birth canal.

In breastfeeding populations, postnatal exposure could account for 40% of all transmissions. Studies suggest that transmission risk in infants who are exclusively breastfed is half that of infants who are given mixed feeding.³

Malaysia introduced antenatal counselling and testing for HIV in 1998 and utilized the Paediatric AIDS Clinical Trials Group (PACTG) 076 protocol for its PMTCT programme. From its introduction to the end of 2006, almost 3 million pregnant women were screened, representing 99.5% coverage of all recorded pregnancies. The prevalence of HIV-1 infection among pregnant women has remained an average of 0.036% over this time with an estimated average perinatal transmission rate of 3.7% (median 3.95%)².

In developed countries, the number of children of HIV positive mothers newly infected with HIV has decreased dramatically with a perinatal transmission rate of <1% - a result of antiretroviral (ARV) prophylaxis and the use of highly active antiretroviral therapy (HAART) for pregnant HIV infected mothers, the selection of lower risk delivery practices, neonatal ARV prophylaxis, and lower risk approaches to infant feeding.

Although studies and advances in the management of HIV infection among children and adolescents have lagged behind those in adults, there have been substantial advances in the diagnosis, evaluation, treatment and monitoring of children exposed to and infected with HIV-1.

In Malaysia, limited paediatric formulations have been made available by the MOH free of charge for patients and have enabled the provision of at least first and second line ARV drugs for children.

Ongoing advances and research in PMTCT and the development of new ARV drugs and improvements in strategies of ARV management are occurring at rapid pace. Major online references are provided and the reader is advised to look these up to obtain the latest data and information on advances in HIV in children and adolescents.

This CPG addresses two broad clinical areas.

- The management of the infant with perinatal exposure to HIV infection
- The management of HIV infection in children and adolescents.

2. MANAGEMENT OF THE PERINATALLY EXPOSED INFANT

2.1 HIV PROPHYLAXIS

PREVENTION OF MOTHER -TO- CHILD TRANSMISSION (PMTCT)

In the absence of any intervention, the risk of MTCT is between 15 and 45%. However, several effective prevention measures have been identified that can reduce the transmission rate to less than 2%. These interventions include ARV prophylaxis or HAART given to HIV-1 infected pregnant mothers, ARV prophylaxis for their newborn babies, safer approaches to delivery (including elective caesarean section) and total substitution of breastfeeding with infant formula.

The Pediatric AIDS Clinical Trials Group (PACTG 076) protocol ^{4, Level 2} was the first major study to demonstrate the effectiveness of a 3-part (antenatal, intrapartum and neonatal) ZDV prophylactic regimen in reducing the MTCT by 68%. The protocol was rapidly adopted by many countries (including Malaysia in 1998), resulting in significant reduction in numbers of infected infants. Over the years, many more trials have been conducted to evaluate different ARV prophylactic regimens to reduce MTCT both in breastfeeding and non-breastfeeding populations. These trials have confirmed the efficacy of various regimens including ZDV alone, ^{5, Level 2; 6, Level 2; 7, Level 2; 8 Level 2; 9, Level 2; 10, Level 6; 11, Level 1}, ZDV + Lamivudine (3TC) ^{12, Level 2; 13 Level 2; 14, Level 2; 15, Level 6}, single-dose nevirapine (sdNVP) ^{16, Level 2; 17, Level 2} and more recently, combinations of ZDV + sdNVP ^{18, Level 2; 19, Level 6}, ZDV + 3TC + sdNVP ^{22, Level 9} and triple ART/HAART. ^{20, Level 6; 21, Level 6}

Although several ARV regimens have been studied using different durations of either single or combined drugs, questions still remain regarding which regimen is the best in achieving the largest reduction in MTCT. Direct comparisons between studies are often difficult as studies are done using various methodologies and are conducted in different study populations.

Despite these limitations, several conclusions can be drawn from the findings of these studies:

PREVENTION OF MOTHER TO CHILD TRANSMISSION (PMTCT)

Three components of treatment or prophylaxis (i.e. antenatal, intrapartum and neonatal) are important as each component contributes towards reduction in the risk of mother- to-child transmission (MTCT).

Longer courses of antenatal antiretroviral (ARV) prophylaxis or therapy beginning earlier in pregnancy are more efficacious in reducing MTCT. Longer ARV prophylaxis for the infant is not a substitute for longer duration of the maternal antenatal component. However, regimens that provide longer infant prophylaxis appear to be beneficial if the mother has received less than 4 weeks of HAART or ARV prophylaxis before delivery.

Combination regimens are generally more efficacious than a single-drug regimen.

Exposure to antiretroviral therapy or prophylaxis may induce development of viral resistance towards the drugs used (especially nevirapine, but also lamivudine) in mothers and potentially also in their infants; this may limit the choice or efficacy of antiretroviral therapies during the 6 to 12 months following delivery.

Adequate counselling, support and monitoring to ensure adherence to the prescribed ARV regimen and chosen method of infant feeding are essential to PMTCT program success.

Four commonly encountered perinatal scenarios and the recommended approaches to ARV prophylaxis for PMTCT are discussed below:

According to the Malaysian CPG on Management of HIV Infection in Pregnant Women (2008)^{23, Level 9}, women with World Health Organisation (WHO) stage 3 or 4 disease or with CD4 lymphocyte counts less than 250 per mm³ at diagnosis should be commenced on HAART, while those who are asymptomatic and with CD4 cell counts more than 250 per mm³ at diagnosis are given short term antiretroviral therapy (START).

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

The risk of MTCT in this group is low but not negligible and depends on the degree of viral suppression in the mother. The duration of ZDV for the infant is based on the data extrapolated from PACTG 076 study.

As the evidence for the optimal duration of infant component of ZDV is still inconclusive, the current recommendations differ from country to country, ranging from one week in some countries to four to six weeks in others.^{22, Level}

9; 24, Level 9; 25, Level 9

Scenario 1 - Recommendation for newborn infant whose mother is on HAART

The newborn infant should receive zidovudine* syrup immediately after birth and this is continued for a total duration of 6 weeks. **(Grade B)**

* Dosing according to maturity - Refer Appendix 4

Scenario 2: HIV infected pregnant mother on single agent ZDV prophylaxis (commenced between 14-28 weeks)

The PACTG 076 study of ZDV versus placebo showed a 68% reduction in transmission in non-breastfeeding infants. A randomized trial in Thailand 26, Level 2 exploring a less complex regimen using a shorter course of ZDV (for mother from 36 weeks, with oral ZDV intrapartum and no ZDV for infant) showed a lower efficacy (50% reduction). The Perinatal HIV Prevention Trial (PHPT-1) ^{5, Level 2} evaluated four different durations of antepartum and neonatal administration of ZDV and showed in utero transmission was significantly higher with short (starting at 36 weeks) vs long (starting at 28 weeks) maternal prophylactic regimens (5.1% vs. 1.6%).

Scenario 2 - Recommendation for newborn infant whose mother commenced single drug zidovudine prophylaxis (between 14-28 weeks)

The newborn infant should receive zidovudine* syrup immediately after birth and this is continued for a total duration of 6 weeks. **(Grade A)**

* Dosing according to maturity - Refer Appendix 4

Scenario 3: HIV infected pregnant mother at delivery who has not received adequate antenatal antiretroviral prophylaxis or therapy (less than 4 weeks)

Among pregnant women who had not received any antenatal ARV drugs, intrapartum and postpartum prophylaxis using different ARVs have been shown in randomized trials to be efficacious in reducing MTCT. The HIVNET 012 study ^{16, Level 2; 27, Level 2} comparing sdNVP vs ZDV to mothers and infants showed a 42% reduction in MTCT in the sdNVP group. The SAINT trial in South Africa ^{13, Level 2} which compared sdNVP with ZDV/3TC noted no significant difference in transmission rate between the two regimens.

A meta-analysis ^{28, Level 1} of individual records of data from African MTCT prevention trials indicated that a combination of ZDV and 3TC started during labour has similar efficacy to sd-NVP in preventing MTCT.

The choice of ARV prophylaxis for the newborn infant will depend on the ARV regimen received by the mother. The Malaysian CPG on Management of HIV Infection in Pregnant Women (2008)^{23, Level 9} recommends that an HIV infected mother who presents in labour and who has not commenced HAART or ARV prophylaxis be given a combination of ZDV/3TC + sdNVP during the intrapartum period. If Lower Segment Caesarean Section (LSCS) can be performed, the mother receives intravenous (IV) ZDV only. The newborn infant receives sdNVP as soon as possible after birth and six weeks of ZDV. The recommendation to add six weeks of ZDV is extrapolated from the PACTG 076 and the PHPT-1 studies, which demonstrated that longer duration prophylaxis was more effective than a shorter course for the infant if the mother had received ARVs for less than four weeks.

Scenario 3 - Recommendation for newborn infant whose mother has not received adequate antenatal antiretroviral prophylaxis or therapy (none or less than 4 weeks)

The newborn infant should be given single dose nevirapine (sdNVP) at birth **and** zidovudine* for a duration of 6 weeks. The medications should be given immediately after birth. **(Grade B)**

* Dosing according to maturity - Refer Appendix 4

Scenario 4: Infant born to HIV infected mother who has not received any (antenatal or intrapartum) ARV prophylaxis or therapy

When the mother presents late with unknown status or the baby is found abandoned, rapid testing is recommended. ARV prophylaxis is instituted immediately on a positive screening test and the rapid test result confirmed by standard HIV-1 testing.

Three studies have examined the situation where HIV infected mothers were diagnosed late and had not received antenatal or intrapartum ART. A cohort study in New York^{29, Level 6} found that administration of ZDV to a newborn infant for 6 weeks was associated with a reduction in transmission, compared with no intervention, provided that it was given within 48 hours of delivery (transmission rate 9.3% vs. 26.6%). A South African trial^{30, Level 2} in mixed feeding infants comparing sdNVP with six weeks of ZDV showed no difference in transmission rate at 12 weeks. A randomized trial in Malawi^{31, Level 2} in a breastfeeding population compared newborn post-exposure prophylaxis where newborn received either sdNVP or sdNVP + ZDV for 1 week. At 6-8 weeks, transmission rate was 20.9% and 15.3% ($p=0.03$), respectively - showing an efficacy of 36% in the combination arm. Thus a combination of sdNVP and zidovudine is recommended for infants whose

mothers had not received any ARTs and based on data extrapolated from the PHPT-1 study longer course of ZDV (4 weeks) for infants are more efficacious.

Scenario 4- Recommendation for newborn infants whose mothers have not received any antiretroviral therapy (antenatal or intrapartum)

Newborn infants should receive single dose nevirapine at birth and zidovudine* for 6 weeks. The medications should be given immediately after birth. **(Grade B)**

The medications may still be beneficial if given within 48 hours. **(Grade B)**

* Dosing according to maturity - Refer Appendix 4

2.2 EVALUATION & CARE AT BIRTH

Babies born to HIV infected mothers who were diagnosed before pregnancy or during the antenatal period are likely to be exposed to ART PMTCT or as part of maternal therapy. In such situations there may be concerns about possible adverse effects of maternal ART on the foetus. In addition, mothers may have co-existing infections, in particular sexually transmissible infections (STIs) and tuberculosis (TB) thus exposing the foetus and neonate to such infections.

A Swiss study reported a possible association between multiple ART and preterm labour,^{32, Level 6} although this was not observed in another study involving a larger number of HIV infected mothers.^{33, Level 6} The latter study however, seems to suggest a significant difference in the rate of very low birth weight (VLBW) infants in those mothers who received a protease inhibitor (PI) compared to those who did not. The European Collaborative Study^{34, Level 6}, in its analysis of 3740 mother-infant pairs with 1973 infants exposed to ART (including 602 exposed to HAART) enrolled between 1986 and 2003 identified 1.6% (31 of 1973) as having various congenital abnormalities. Congenital abnormalities were also noted in 1.4% (24 of 1767) unexposed children. Concerns have been noted regarding an association between first trimester efavirenz exposure and neural tube defects based on a study in monkeys and case reports in humans.^{23, Level 9}

Thus to date, current evidence suggests that there is no apparent increase in any particular abnormality with the use of ART or HAART during pregnancy. With expanded use and development of new ARV drugs however, further monitoring and research are necessary to assess the teratogenic and other risks of use of combinations of antiretroviral and other drugs at the time of conception or in early pregnancy.

The majority of cases of HIV infection from mother-to-child occur at the time of delivery and these babies are usually asymptomatic at birth. Therefore the findings of hepatosplenomegaly and lymphadenopathy at birth are unlikely to be due to HIV infection and may reflect other pathology. Such signs with or without low birth weight therefore warrant a search for causes other than HIV infection.

Recommendation for evaluation at birth

All perinatally exposed infants should receive standard neonatal evaluation and care. **(Grade C)**

2.3 INVESTIGATIONS AT BIRTH

Investigations are done at birth to exclude possible side effects of in-utero exposure to ARVs, to exclude common co-infections that may have been transmitted to the infant and to determine the infant's HIV infection status.

2.3.1 Possible adverse effects of maternal ART

A Swiss cohort study^{32, Level 6} and a European collaborative study^{34, Level 6} showed that ZDV exposure in foetal or neonatal life was strongly associated with a diagnosis of anaemia. However in all cases, haemoglobin levels reverted to normal when ZDV was discontinued.^{32, Level 6; 34 Level 6; 24, Level 9} A full blood count (FBC) should be performed immediately on the newborn infant as a baseline evaluation before administration of neonatal ZDV and repeated at 6 weeks after completion of the ZDV regimen. If abnormal, repeat measurement should be performed at age 12 weeks. Infants who have anaemia at birth or who are born prematurely warrant more intensive monitoring of FBC.^{24, Level 9}

Data are limited concerning potential toxicities in infants whose mothers have received combination antiretroviral therapy. More intensive monitoring of haematologic and serum chemistry measurements during the first few weeks of life is advised for these infants.^{24, Level 9}

2.3.2 Co-Infections

HIV infected mothers may be exposed to other infectious diseases in particular STIs, TB, toxoplasmosis, syphilis, cytomegalovirus (CMV), Herpes simplex and Hepatitis B and C infections. There is also a risk that latent infections could be reactivated in the immunocompromised mother and transmitted to the newborn. However, there is very little knowledge on the relative risk of such transmission from mother-to-infant with the exception of Hepatitis C virus (HCV). In the meta-analysis by Bonacini,^{35, Level 1} HCV co-infected mothers were significantly more likely to transmit HCV to their children.

There are conflicting reports on the risk of in-utero transmission of CMV in HIV-1 infected infants.^{36, Level 6; 37, Level 6} The only common finding in these two studies was that HIV infected infants with in-utero CMV infection experienced rapid disease progression.

There is a paucity of data on vertical transmission of toxoplasmosis. The only study reported the transmission from a chronically infected mother to infant was uncommon.^{38, Level 9}

The transmission rate of Hepatitis B virus (HBV) from a surface antigen (HBsAg) positive mother to her infant appears to follow the same pattern as non-HIV infected mother.^{39, Level 9}

One large US cohort conducted from 1988-1994 reported the rate of congenital syphilis to be substantially higher amongst babies born to HIV infected women than when the mother was HIV negative.^{40, Level 6}

Congenital TB has been reported among children born to HIV infected women with active TB.^{41, Level 6} However, the true incidence and whether the transmission rate is higher among these children compared with children born to non HIV infected women with active TB are unknown.^{42, Level 9}

At the time of birth, maternal health information should be reviewed to determine if the infant may have been exposed to maternal co-infections such as TB, syphilis, hepatitis B or C, CMV, toxoplasmosis and herpes simplex virus. Appropriate and standard diagnostic testing of the infant should be undertaken and treatment provided based on maternal findings.^{43, Level 9}

2.3.3 HIV infection

All newborn infants born to HIV infected women, will have transplacentally transferred antibodies at birth which will take many months to clear (median age of seroreversion is 10 months).^{44, Level 6} Therefore antigen-based investigations are required to definitively diagnose HIV in young infants.^{45, Level 6; 46, Level 9}

HIV DNA PCR is a sensitive technique used to detect specific HIV viral sequences in integrated proviral HIV DNA in a patient's peripheral blood mononuclear cells (PBMCs). The sensitivity of a single HIV DNA PCR test performed at <48 hours of age is less than 40%, but increases to over 90% by 2-4 weeks of age.^{45, Level 6; 46, Level 9; 47, Level 1; 48, Level 8; 49, Level 6}

Currently available HIV-1 DNA PCR tests are less sensitive in the detection of non-subtype B HIV, and false-negative HIV-1 DNA PCR assays have been reported in infants infected with non-subtype B HIV.^{50, Level 9; 48, Level 8}

Non-subtype B viruses predominate in some parts of the world, such as subtype E in much of Southeast Asia. In Malaysia, a study amongst

injecting drug users (IDUs) found a predominance of subtype B in more than 90% of the subjects.^{51, Level 8} However a more recent study in a similar population (i.e. IDUs) demonstrated that subtype B was present in 50.0% followed by CRF01_AE/B recombinant in 41.7%.^{52, Level 8}

HIV RNA assays detect extracellular viral RNA in the plasma and are as sensitive and specific as HIV DNA PCR for early diagnosis of HIV infection in HIV-exposed infants.^{53, Level 6; 54, Level 6; 46, Level 9} However no HIV RNA PCR test is currently licensed in Malaysia for use in diagnosing infection.^{55, Level 9}

The use of the currently approved HIV p24 antigen assay is not recommended for infant diagnosis because of its lower sensitivity compared to other virologic tests.^{46, Level 9; 48, Level 9; 56, Level 8}

In general, HIV-1 DNA PCR assay is the preferred diagnostic test. The birth specimen must be a neonatal, not a cord blood sample.^{46, Level 9} The reference laboratory (Institute for Medical Research) requests that the first sample should be sent with mother's sample for antibody re-testing.

Recommendation for investigations at birth

A Full Blood Count (FBC) should be performed on the newborn as a baseline evaluation before administration of zidovudine and repeated at 6 weeks after completion of the zidovudine regimen. If abnormal, repeat measurement should be performed at age 12 weeks. **(Grade B)**

Infants who have anaemia at birth or who are born prematurely warrant more intensive monitoring of FBC. **(Grade C)**

At the time of birth, review maternal health information to determine if the infant may have been exposed to maternal co-infections such as tuberculosis, syphilis, toxoplasmosis, cytomegalovirus, Herpes simplex and Hepatitis B and C infections. Diagnostic testing and treatment of the infant are based on maternal and infant findings. **(Grade C)**

HIV DNA PCR test should be carried out at 14-21 days of age (and at subsequent intervals - see Section 2.7) **(Grade C)**

2.4 ADVICE AND COUNSELLING

Counselling and support to address the numerous possible problems faced by the HIV positive mother are a necessary part of management. Possible problem areas that should be addressed include social, family, domestic violence, financial status and unemployment among others.

New parents of an HIV exposed infant would also require information, support and advice on medical care for the infant. Such counselling should

ideally commence in the antenatal period. Important topics to cover include risk of transmission, medications to prevent perinatal acquisition of HIV and PCP prophylaxis, infant feeding advice (and especially the importance of avoiding mixed breast and formula feeding), importance of and schedule for follow-up visits, diagnosing infection, clinical assessment and laboratory tests, availability of formula for the poor, immunization advice, need for prompt evaluation when ill, and of assurances that the health service will maintain confidentiality.^{43, Level 9}

Recommendation for counselling parents/caregivers of HIV-exposed infant

Paediatricians should provide counselling to parents and caregivers of HIV-exposed infants about HIV infection, future care, diagnostic tests, infection-control measures, care of the infant including feeding, immunisations and potential drug toxicity. **(Grade C)**

2.5 FEEDING

A systematic review involving two meta-analyses, one randomised controlled trial (RCT) and one observational study showed that breastfeeding was associated with an increase of vertical transmission of 14% and 16%. Even in women who received antiretroviral drugs, breastfeeding significantly increased the MTCT rate.^{57, Level 1}

A large RCT enrolling 425 HIV infected, antiretroviral naïve pregnant women and randomizing mother-infant pairs to breastfeeding (n = 212) vs. formula feeding arms (n = 213) showed the cumulative probability of HIV-1 infection at 24 months was 36.7% in the breastfeeding arm and 20.5% in the formula arm, giving an estimated rate of breast milk transmission of 16.2%.^{58, Level 2}

Most transmission through breast milk occurred early although transmission continued throughout the duration of exposure.^{59, Level 6; 60, Level 2} Diarrhoeal illness and pneumonia occurred at similar rates, regardless of the mode of feeding.^{61, Level 2} More recent studies done in countries with high infant mortality rates have shown that cumulative infant mortality rates are significantly higher for the formula-fed group than for the exclusively breastfed infants.^{62, Level 6; 60, Level 6}

A cohort study of 549 children born to HIV infected women in Africa demonstrated that mixed feeding carried a higher risk of HIV transmission to the baby compared to exclusive breastfeeding or artificial feeding in babies less than 3 months of age.^{67, Level 6}

Where replacement feeding is acceptable, feasible, affordable, safe and sustainable (AFASS), most guidelines recommend that HIV infected mothers should not breastfeed their infants.^{63, Level 9; 43, Level 9; 64, Level 9, 65, Level 9}

A Ministry of Health Malaysia circular states that infant formula be made available to infants below 6 months from low families (income <RM1200) in the first instance and case to case basis for such infants whose families income is >RM1200.^{66, Level 9}

Recommendation for feeding

All HIV infected mothers should be advised not to breastfeed their infants as it is associated with a significant risk of vertical transmission. **(Grade A)**

It must be ensured that replacement feeding is acceptable, feasible, affordable, sustainable, and safe **(Grade C)**

In the absence of a safe alternative to breast milk, exclusive breastfeeding is recommended during the first 6 months. **(Grade B)**

Families should be counselled against mixed feeding at any time, as it carries a higher risk of MTCT than exclusive breastfeeding or replacement feeding **(Grade B)**

2.6 IMMUNISATION

The following section will discuss the available evidence on the safety, immunogenicity and effectiveness of various vaccines in HIV infected infants and children.

a) BCG

Administration of Bacille Calmette-Guérin (BCG) to HIV infected infants in the first month of life is associated with low rates of complications because immune suppression takes several months to develop.^{67, Level 6} Complications arising from BCG vaccination include lymphadenitis, disseminated infection and immune reconstitution inflammatory syndrome (IRIS).

- The rates of complications have been similar in HIV infected and HIV-uninfected infants, but lymphadenitis has been more severe in HIV infected children.^{68, Level 6; 69, Level 8; 70, Level 6; 71, Level 6; 72, Level 6; 73, Level 8; 74, Level 9}
- Disseminated BCG infection has been reported in HIV infected children.^{75, Level 8; 76, Level 8}
- IRIS (in the form of severe inflammation and/or ulceration at the BCG injection site) has been reported in HIV infected infants and children after commencement of HAART.^{78, Level 7}

Immunogenicity of BCG is difficult to assess as there is no good marker. In a cohort study in Rwanda, tuberculin skin test was positive in only 37% of HIV infected infants compared to 70% in infants born to HIV-uninfected mothers.^{71, Level 6} There are very little data on the effectiveness of BCG in HIV infected children. A small case control study^{77, Level 7} did not show any protection, but the study did not have sufficient power to detect possible protection against TB meningitis or military TB. Two adult studies showed some benefit in HIV infected adults who had received BCG during childhood. Marsh et al^{78, Level 7} noted adults with clinical AIDS in Trinidad who received BCG during childhood have a reduced risk of developing bacteremic TB (2% vs 10%). Arbelaez et. al^{79, Level 7} found overall 22% protection from all forms of TB.

b) Polio

Oral Polio Vaccine (OPV) is a live-attenuated vaccine. Vaccine-associated paralytic poliomyelitis (VAPP) is a serious but fortunately rare complication of the vaccine. Despite its extensive use in many countries in the world, there have only been 2 case reports of HIV infected children developing VAPP after OPV.^{80, Level 9; 81, Level 9} In contrast, Inactivated Polio Vaccine (IPV) is not associated with VAPP. Although the risk to the child following OPV may be low, he/she may continue to excrete virus in the stools for some weeks after vaccine. This may pose potential risk to close contacts who may be immunocompromised (e.g. parents or siblings who may be HIV infected). Thus it is recommended that IPV be given to HIV affected or infected children. IPV is provided free on request from any government health clinic.

Both vaccines are immunogenic and in studies >90% of HIV infected children developed protective antibodies after 3 doses of the vaccine although the geometric mean antibody titre (GMT) was lower than in non-infected individuals.^{69, Level 6; 82, Level 6}

c) Measles, Mumps, and Rubella (MMR)

MMR vaccine is a live-attenuated vaccine. The risk of adverse reactions following vaccination was no different for HIV infected (treated and untreated) and uninfected children.^{83, Level 6; 84, Level 6, 85, Level 6; 86, Level 6; 87, Level 8} Only one serious adverse event has been reported in a HIV infected man with a CD4 lymphocyte count <200 at the time when he received his second dose of MMR: he developed measles-vaccine pneumonitis and died.^{88, Level 9} No serious adverse event has been reported with mumps and rubella vaccines.

Studies on the immunogenicity of MMR vaccine in HIV infected children noted impairment of antibody response with only half developing protective antibody level after primary immunisation and their antibody also waned faster than in non-infected individuals.^{89, Level 6; 87, Level 8; 85, Level 6} Response to repeat immunization was variable but generally poor.^{90, Level 8; 91, Level 9}

There are minimal data on the protective efficacy of MMR vaccine in HIV infected individuals. Experience in African countries has noted a reduction in measles incidence in regions with high HIV prevalence by maintaining high immunisation rates and periodic supplementary campaigns.^{92,Level 9}

d) Hepatitis B

Hepatitis B vaccine is a recombinant vaccine. No significant adverse events were noted in cohort studies of infants receiving primary immunisation from birth.^{93,Level 6;94,Level 6}

Studies on the immunogenicity of hepatitis B vaccine have demonstrated poorer response rate in HIV infected infants and children with only 25-50% developing protective antibodies after primary immunisation.^{95,Level 6;96,Level 6;97,Level 6;98,Level 6} Booster doses or higher doses have not been found to be immunogenic.^{99,Level 6;98,Level 6} There are no studies of the protective efficacy of hepatitis B vaccine in HIV infected children.

e) Haemophilus influenzae type B (Hib)

Hib is a conjugated polysaccharide vaccine. The vaccine is safe and immunogenic in HIV infected infants and children (although the immunogenic response is less than that seen in normal children).^{99,Level 4; 100,Level 6; 101,Level 6} Two recent studies from South Africa suggest that Hib vaccine is effective in protecting from invasive Hib disease although the level of protection is lower than that seen in uninfected children (43.9-54.7% vs 83-90.8%).^{102,Level 6;103, Level 6}

f) Diphtheria, Tetanus, Pertussis (DTP)

DTP vaccine is safe and immunogenic in HIV infected infants and children.^{82, Level 6;69,Level 6; 104,Level 6; 105,Level 6} However, GMTs achieved were lower than those in non-infected infants. There is no rigorous study on the protective efficacy of DTP vaccine in HIV infected children.

g) Pneumococcal vaccine

Children infected with HIV have a markedly increased risk of pneumococcal infection - from 2.8 to 12.6 times the rate compared with those who are not HIV infected.^{106, Level 8;107,Level 6;108,Level 6; 109,Level 7}

Both pneumococcal polysaccharide (PPV) and pneumococcal conjugate vaccines (PCV) are safe in HIV infected infants and children.^{110, Level 4; 111, Level 4 ;112, Level 6} Approximately 65-100% of HIV infected children developed protective antibody after vaccination with PCV but GMTs achieved were lower than those in uninfected children.^{113, Level 6; 112, Level 6; 111, Level 4}

The response to the polysaccharide vaccine is generally poorer than to the conjugate vaccine.^{111, Level 6; 115, Level 6} A large RCT from South Africa showed PCV provided 65% protection against invasive pneumococcal disease among HIV infected infants.^{116, Level 2}

In a retrospective case-control study among adults from Spain^{117, Level 6}, ART and PPV were found to have a significant, independent protective effect against pneumococcal disease, regardless of CD4 lymphocyte count. It was therefore concluded that all patients (adults) with HIV infection should be vaccinated with PPV vaccine to prevent pneumococcal disease.

Table 1: Pneumococcal Vaccination Schedule for Children at Special Risk

Age	2-6 months	7-11 months	12-23 months
Conjugate vaccine	3 doses, monthly intervals	2 doses, monthly intervals	2 doses, 2 months apart
	Further dose in second year of life		
Polysaccharide vaccine	Then after 2 nd birthday single dose of 23-valent		

When both conjugate and polysaccharide vaccines are used, the polysaccharide vaccine should be given at least two months after the last dose of conjugate vaccine

h) Meningococcal vaccine

So far, there are no data available on the response of HIV infected infants and children to meningococcal polysaccharide or conjugate vaccines.

i) Varicella vaccine

This is a live-attenuated vaccine. The vaccine is safe and thus far, no increase in adverse reactions compared to normal controls have been noted.^{118, Level 6; 119, Level 6} However, the studies on safety excluded those with severe immunosuppression. The vaccine induced good immunogenicity in HIV infected children with 60-79% developing protective antibody 2 months after completion of 2-dose vaccination.

j) Human Papilloma Virus Vaccine

There is evidence that infections with higher risk human papillomavirus (HPV) sub-types are more common in HIV infected girls aged 13-19 years than in HIV non-infected girls of the same age. The rates of squamous intraepithelial lesions were significantly higher in the HIV infected girls.^{120, Level 2}

The HPV vaccine is indicated in girls and women 9 to 26 years of age for the prevention of cervical cancer, precancerous or dysplastic lesions, and genital warts caused by HPV Types 6, 11, 16, and 18. No recommendations have been made regarding the use of HPV vaccinations in HIV-positive individuals. Clinical trials are currently underway to assess the safety and efficacy of the vaccine in individuals with HIV. It should be noted that the candidate vaccines are preventive rather than therapeutic, the benefits of the vaccine in individuals who have already been exposed to HPV are doubtful.

^{121, Level 2}

k) General considerations for immunisation

In general, vaccines may be less effective in HIV infected children due to their impaired immune response. Even after appropriate vaccination, the child may still be susceptible to vaccine preventable diseases and should therefore be given appropriate preventive therapy after exposure to these diseases where available.

Immunisation with live vaccines carries a risk of causing disease in the immunocompromised host in addition.

Recommendations for immunisation in HIV infected infants and children must take into account available data on the safety, immunogenicity and effectiveness of each vaccine in this special group of children. A recent review provides a relevant and detailed discussion of these issues.^{92, Level 9}

Recommendation for routine childhood immunisation

All infants born to HIV infected mothers should receive routine childhood immunisation at the usual recommended age. **(Grade B)**

The following precautions are recommended for live-attenuated vaccines:

- **BCG** should not be given in *symptomatic* HIV infected infants or children (WHO Stage 2, 3, 4) as they are at higher risk of developing disseminated disease. **(Grade B)**
- **OPV** should be replaced by injectable Inactivated Polio Vaccine (IPV). **(Grade C)**
- **MMR** should be given as per schedule except to those who have severe immunosuppression (CD4 < 15%) **(Grade C)**
Refer to Appendix 4 on age-related immunological criteria

Additional vaccines:

Pneumococcal polysaccharide vaccine - a single dose should be given to HIV infected child over 2 years of age. **(Grade C)**
(Refer to Appendix 7)

Where available all HIV infected children below 5 years of age should receive **pneumococcal conjugate vaccine**. **(Grade B)**
(Refer to Appendix 7)

Varicella vaccine should be offered to an HIV infected child ≥ 12 months of age without history of varicella in WHO Clinical Stage 1, 2 or 3 and with CD4 $\geq 15\%$. Two doses of varicella vaccine at a minimum interval of 3 months should be given. **(Grade C)**

Table 2: IMMUNISATION SCHEDULE FOR HIV INFECTED INFANTS AND CHILDREN

Vaccine	Asymptomatic	Symptomatic	Comment
BCG	Recommended	Omit*	
Hepatitis B	Recommended	Recommended	
DTP	Recommended	Recommended	
Hib	Recommended	Recommended	
OPV	Omit	Omit	Replace with IPV
IPV	Recommended	Recommended	
MMR	Recommended	Recommended*	
Varicella	Recommended	Recommended*	
Pneumococcal Polysaccharide Vaccine (PPV)	Recommended	Recommended	Use in children age > 2 years
Pneumococcal Conjugate Vaccine (PCV)	Consider	Consider	Conjugate vaccine is more immunogenic than polysaccharide vaccine. However, they are currently expensive

*Omit if severely symptomatic (WHO Stage 4) or severe immunosuppression (CD4 < 15%)

2.7 CLINICAL AND LABORATORY MONITORING OF THE PERINATALLY EXPOSED INFANT

Clinical, immunological and virological monitoring is done to monitor the well-being of the infant, determine the HIV infection status and, for those who are infected, to determine the timing of initiation of ART and response to therapy.

Clinical monitoring should include:

- Monitoring of physical growth
- Monitoring of developmental milestones
- Early detection of opportunistic infections
- Review of immunization
- Monitoring for adverse effects of drug therapy

2.7.1 Virologic & serologic monitoring

HIV PCR DNA is done at 14-21 days, at 1 - 2 months of age, and at 4 - 6 months of age to determine the infection status.

Serologic testing after 12 months of age is used to confirm that maternal HIV-1 antibodies transferred to the infant in utero have disappeared. If the child is still antibody positive at 12 months of age, then testing should be repeated at 18 months of age. Loss of HIV-1 antibody in a child with previously negative HIV-1 DNA PCR test results definitively confirms that the child is not infected with HIV-1. Positive HIV-1 antibodies at >18 months of age indicates HIV-1 infection.

Definitions/ interpretation of results:

HIV infection is confirmed when:

- HIV virologic tests (HIV DNA PCR) performed on 2 separate blood samples are positive, regardless of age;

OR

- HIV antibody tests using two different methods (enzyme immuno assay (EIA) / particle agglutination (PA)) are positive at ≥ 18 months of age;

OR

- There is a positive HIV antibody test with a confirmatory Western Blot (or Line Immuno Assay (LIA)) at ≥ 18 months of age.

HIV infection can be *presumptively* excluded* in non-breastfed infants with:

- Two or more negative virologic tests (HIV DNA PCR), with one test obtained at ≥ 14 days of age and one obtained at ≥ 1 month of age;

OR

- One negative virologic test result obtained at ≥ 2 months of age;

OR

- One negative HIV antibody test result obtained at ≥ 6 months of age.

HIV infection can be *definitively* excluded* in non-breastfed infants when:

- There are ≥ 2 consecutive negative HIV virologic tests (HIV DNA PCR) performed at ≥ 1 month of age, with one being performed at the age ≥ 4 months,

AND/OR

- There are ≥ 2 negative HIV antibody tests performed at age ≥ 6 months, with an interval of at least 1 month between the tests in an infant with no clinical or virological evidence of HIV infection.

Confirm the absence of HIV infection in infants by documenting:

- Loss of HIV antibody in a child with previously negative virologic tests.

* With no other laboratory (e.g., no positive virologic test results or low CD4 count) or clinical evidence of HIV infection
(Adapted from *Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection* February 28, 2008)

Recommendation for monitoring of the perinatally exposed infant

Clinical monitoring should include:

- Monitoring of physical growth
 - Monitoring of developmental milestone
 - Early detection of opportunistic infections
 - Review of immunization
 - Monitoring for adverse effects of drug therapy
- (Grade C)**

HIV DNA PCR is done at 14 - 21 days; 1 - 2 months; and 4 - 6 months.
(Grade C)

For perinatally exposed infants whose HIV DNA PCR is negative:

- Follow-up should be continued long term. **(Grade C)**
- Seroreversion (positive to negative antibody status) should be documented by 18 months of age. **(Grade C)**

2.8 PRIMARY PNEUMOCYSTIS JIROVECI PNEUMONIA PROPHYLAXIS FOR THE PERINATALLY EXPOSED INFANT

Co-trimoxazole (trimethoprim [TMP], sulfamethoxazole [SMX]) is a widely available, low-cost antibiotic that has been used worldwide for many years in the treatment of community-acquired infections. In HIV infection, it is highly effective for treatment of, and prophylaxis against, *Pneumocystis jiroveci pneumonia* (PCP). PCP is one of the earliest opportunistic infections (OI) to arise with increasing immunosuppression. Studies in Malawi^{122, Level 8} and Zambia^{123, Level 8} have showed that PCP is an important cause for morbidity and mortality in HIV infected infants.

2.8.1 Mortality and Morbidity

Madhi et al^{124, Level 8} showed that primary TMP-SMX prophylaxis from the age of 6 weeks to 1 year significantly reduced death in infant/child admitted with severe PCP. Similarly in a retrospective cohort study,^{125, Level 6} showed that primary prophylaxis was highly effective in decreasing the frequency of PCP and early death. A study by Coutoudis et al,^{126, Level 8} initiating primary TMP-SMX prophylaxis in infants born to HIV positive mothers showed a significant (30%) reduction in lower respiratory tract infections.

In Thailand, introducing a policy of universal primary TMP-SMX prophylaxis for infants born to HIV positive mothers significantly decreased admissions for severe pneumonia. The proportion of PCP cases among children diagnosed with severe pneumonia decreased from 67% (8 of 12) before introduction of the policy to 0% 6 months latter.^{127, Level 5} The data also suggests that PCP prophylaxis can prevent both PCP and non-PCP.

CD4 cell counts are not a good indicator of risk for PCP in infants aged less than one year. Many young infants with PCP have a CD4 cell count more of than 1500. ^{128, Level 9}

2.8.2 Dosages

Various dosages of TMP-SMX have been used for prophylaxis; these are usually based on weight, surface area and age. The report of a WHO Expert Consultation on TMP-SMX prophylaxis in HIV infection recommends a daily dose of TMP 20mg / SMX 100mg for children less than 6 months of age. ^{129, Level 9} Alternatively Chokephaibulkit et al, ^{127, Level 9} successfully used TMP-SMX at a dosage of TMP 150 mg /m²/day divided twice daily for 3 days per week.

2.8.3 Side effects

Chintu reported that skin rash was the main side effect in infants given co-trimoxazole. ^{128, Level 2} Other possible side effects include bone marrow toxicity and hepatotoxicity. ^{129, Level 9} These side effects may be monitored on a clinical basis, using a symptomatic approach. ^{129, Level 9} Co-trimoxazole can be used in infants with G6PD deficiency; however caution is advised. ^{130, Level 9}

2.8.4 Alternatives to TMP-SMX

Dapsone and aerosolized pentamidine are alternatives for children who are intolerant to TMP-SMX. In a randomized, multicentre trial comparing different regimens of dapsone, none of the children in the daily 2mg/kg regimen developed PCP. ^{131, Level 9} The recommended dose of aerosolized pentamidine in children aged 5 years and older is 300 mg once monthly. ^{132, Level 9} However Principi reported that aerosolized pentamidine isethionate delivered by an ultrasonic Fisoneb nebulizer at doses of either 120 mg once monthly or 60 mg every 2 weeks was effective for PCP prophylaxis in infants and children. ^{133, Level 2} There are no direct comparisons of these alternatives with TMP-SMX.

Recommendation for primary PCP prophylaxis using Co-trimoxazole for the perinatally exposed infant

PCP is recommended for infants with indeterminate HIV infection status starting at 4-6 weeks of age until they are determined to be HIV-uninfected or presumptively uninfected with HIV. ***(Grade B)**

Primary TMP-SMX prophylaxis should be continued until at least 1 year of age for HIV infected infants and then re-evaluated. **(Grade B)**

Further use of TMP-SMX prophylaxis (after 1 year of age) will be guided by clinical staging and CD4 percentage. **(Grade C)**

Cotrimoxazole^o Dosage

- TMP 4mg / SMX 20mg per kg daily **(Grade B)**
- OR**
- TMP 150 mg / SMX 750 mg/m²/day divided twice daily for 3 days per week **(Grade B)**

Alternatives to Cotrimoxazole

- Dapsone #
2mg /kg daily **(Grade B)**
- OR**
- Aerosolized pentamidine
Children less than 5 years of age - either 120 mg once monthly or 60 mg every 2 weeks, after a 4-week period of induction therapy at 60 mg/week. **(Grade B)**

* *Initiation of PCP prophylaxis can be avoided if the infant has negative virologic tests at 2 weeks and at 1 month of age or, if prophylaxis was initiated, can be stopped if virologic testing is negative at or beyond 2 months of age.*

° *Cotrimoxazole can rarely induce haemolysis in persons with glucose-6-phosphate dehydrogenase (G6PD) deficiency and caution should be exercised in such cases.*

Dapsone can increase the risk of haemolysis or methemoglobinemia in patients with G6PD deficiency. Screen for G6PD deficiency before starting dapsone.

3. MANAGEMENT OF HIV INFECTED INFANTS, CHILDREN AND ADOLESCENTS

Management of HIV-1 infected children requires monitoring of disease progression, timely commencement of a potent HAART regimen, monitoring of treatment, assessing response and adverse reactions.

3.1 MONITORING DISEASE PROGRESSION

Monitoring of disease progression of the HIV-1 infected child is through clinical, immunological and virological means.

3.1.1 Clinical

There are two major systems for clinical classification of HIV infection in children: the WHO Clinical Classification and the CDC Classification System. The guideline development group has chosen to adopt the WHO classification for Malaysia (refer Appendix 1 and 2).

3.1.2 Immunologic

Immunologic monitoring is done by serial evaluations of the CD4 lymphocyte count and percentage. HIV associated immunodeficiency is defined as not significant, mild, advanced and severe according to age-related cut-off values of CD4% and count (refer Appendix 3).

3.1.3 Virologic

Virologic monitoring is by the use of plasma viral load (pVL) assays. Current methods used are the Roche Amplicor[®] HIV-1 Monitor System - standard and ultrasensitive and the Roche COBAS Taqman HIV-1[®]. The lower limits of detection vary with the type of assay (Amplicor standard <400 copies/mL, Amplicor ultrasensitive <50 copies/mL and AmpliPrep/Taqman <40 copies/mL).

3.2 ANTIRETROVIRAL THERAPY

3.2.1 Effectiveness of HAART

HAART with at least three drugs is associated with long term viral suppression, and sustained clinical and immunological benefits: it has been the standard recommended treatment worldwide since 1996.

Monotherapy and dual ART have been found not to provide sustained viral suppression and are ineffective. They also carry an increased risk of ARV drug resistance and are no longer recommended.

HAART has been shown to provide the following benefits:

- Reduce mortality by 67-80%.^{134, Level 9 ;135, Level 6 ;136, Level 6 ;137, Level 6 ;138, Level 6 ;139, Level 6 ;140, Level 6}
- Halt progression to AIDS by 50%.^{139, Level 6; 140, Level 6; 136, Level 6} However, Doerholt^{135, Level 6} found no change in progression to AIDS in young infants.
- Reduce hospitalization rate by 68-80%.^{134, Level 6 ;135, Level 6 ;137, Level 6; 141, Level 6} However, Bertolli^{141, Level 6} noted a slight increase in hospitalisation in those on HAART, but this association was not noted when analysis was restricted to more recent years (1997-2002).
- Reduce incidence of opportunistic and related infections by 62-93%.^{142, Level 6} Positive impact on child growth and psychomotor development.^{143, Level 6;144, Level 6}

3.2.2 When to initiate therapy

When to start ART in children remains controversial. The only RCT (PREDICT study) investigating the initiation of HAART therapy has just started recruiting participants.

In the absence of evidence from RCTs, recommendations on when to start combination therapy in children (and adults) are based on cohort data that provide an estimate of the risk of progression to AIDS or death based on surrogate markers of infection (i.e. the child's CD4 % and pVL).

An important meta-analysis,^{145, Level 1} of individual data of 3941 children from 17 studies in Europe and US demonstrated short-term risks (12 months) of progression to AIDS or death at different ages based on child's presenting CD4% and pVL, with the former being the stronger predictor (Appendix 3). Progression to AIDS or death also differs according to age, with infants and young children having a significantly higher risk. In addition, both CD4% and pVL are poorly predictive of disease progression in infants <12 months of age, hence the recommendations for starting ART are usually more aggressive in young infants.

This needs to be balanced against the safety and tolerability of HAART, lack of data on the pharmacokinetics of HAART in young infants and the difficulty in achieving viral suppression in view of the high viral load commonly seen in young infants. Faye^{146, Level 6} in a small cohort of 31 infants, found only 50% of those on HAART had VL suppression (pVL<500) at 6 months and only 18% at 24 months, highlighting the difficulty in sustaining VL suppression in young infants. A PENTA 7 study^{147, Level 6} of 20 infants started on stavudine (d4T) / didanosine (ddI) / nelfinavir (NFV) combination HAART showed good clinical and immunological response at 72 weeks but high rate of virological

failure (n=14) and resistance (n=6). This was attributed to unreliable plasma levels of NFV in young infants. More recent studies suggest the need for higher doses of both NFV and NVP to achieve better viral suppression in young infants.

There is some evidence to suggest that very early treatment of confirmed HIV infected infants is feasible and moderately effective regardless of CD4% or cell counts. Faye^{148, Level 6} noted that young infants who started HAART <6 months did not show early progression to clinical HIV-related disease when compared to 6 of 18 who started treatment after 6 months of age. Luzuriaga^{149, Level 6} found that young infants who started on quadruple HAART (d4T/3TC/NVP/NFV) before 3 months of age tolerated the medications well and had improved long term viral suppression when compared with those started after age 3 months.

In children more than one year of age the risk of disease progression is less than in infants but remains higher than in adults.^{145, Level 1} The response to HAART may also differ with age. In a United Kingdom cohort study^{150, Level 6} of 354 children commencing HAART, greater rises in CD4 cell count were noted in younger children and those with the lowest CD4% at treatment initiation but a better virological response was noted in older children irrespective of their pre-HAART viral load. However, children who started HAART only after they developed severe immunosuppression (CD4 <15%) had poorer outcome than those starting HAART earlier.^{151, Level 8 ; 152, Level 6}

A detailed clinical evaluation is essential prior to initiating HAART and should aim to assess the clinical stage of HIV infection, identify past HIV-related illnesses, identify current HIV-related illnesses that would require treatment and identify co-existing medical conditions and treatments that may influence the choice of therapy.

The decision about when to start ART must also involve evaluation of the whole child and his social environment. The ability of the caregiver and child to adhere to the regimen must be fully assessed and support provided if ART is to succeed. Issues regarding home environment, social, schooling and financial status that may affect adherence to the regimen must also be addressed first before commencing HAART.^{153, Level 9; 154, Level 9; 46, Level 9} Failure to adhere to the regimen will allow continued viral replication and subsequent emergence of drug resistant strains with eventual treatment failure.

Evaluation prior to initiating antiretroviral treatment

Carry out a detailed clinical evaluation prior to initiating antiretroviral therapy to assess the clinical stage of HIV infection, identify past HIV-related illnesses, identify current HIV-related illnesses that would require treatment and identify co-existing medical conditions and treatments that may influence the choice of therapy.

Fully assess the ability of the child and the caregivers to adhere to the treatment before initiating HAART regimen.

Intensive education of the child and caregivers about the importance of adherence to regimen should be provided before therapy is initiated.

Recommendation for when to initiate treatment

Ensure that the child and caregivers will be adherent to the HAART regimen. **(Grade C)**

HIV infected infants < 12 months

Initiate HAART in infants who are symptomatic (WHO Stage 2, 3 or 4) irrespective of CD4 or viral load **(Grade B)**

Initiate HAART in infants who are asymptomatic (WHO Stage 1 *and* CD4<25%) **(Grade B)**

HIV infected children > 1 year

Initiate HAART in children with AIDS or significant symptoms (WHO Stage 3* or 4) irrespective of CD4 and viral load **(Grade B)**

Initiate HAART in asymptomatic or mildly symptomatic children (WHO Stage 1 or 2) who have met age-related CD4 threshold for treatment (refer to Table 2 for details) **(Grade B)**

Consider HAART in asymptomatic or mildly symptomatic children (WHO Stage 1 or 2) who have *either* met age-related CD4 threshold (refer Appendix 4) or have viral load > 100,000 copies (see Table 2) **(Grade B)**

Defer HAART in asymptomatic or mildly symptomatic children (WHO Stage 1 or 2) who have no immune suppression and viral load <100,000 copies/ml. **(Grade B)**

* 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%. (Age-related CD4 values - see Appendix 3)

Table 3 - Guidelines for the use of ARV agents in Pediatric HIV infection. (Adapted from ^{46, Level 9})

Age	Initiate Treatment	Consider	Defer
<12 months	<ul style="list-style-type: none"> Symptoms (WHO Stage 2,3,4) OR Asymptomatic (WHO Stage 1) and CD4 <25% 	<ul style="list-style-type: none"> Asymptomatic (WHO Stage 1) and CD4 < 25% 	
1-<3 years	<ul style="list-style-type: none"> AIDS or significant HIV-related symptoms (WHO Stage 3* or 4) OR Asymptomatic or mild symptoms (WHO Stage 1 & 2) <u>and</u> CD4 <15% 	<ul style="list-style-type: none"> Asymptomatic or mild symptoms <u>and</u> <ul style="list-style-type: none"> CD4 20-24 % or - VL >100,000 copies /ml 	<ul style="list-style-type: none"> Asymptomatic <u>and</u> <ul style="list-style-type: none"> - CD4 >25 % <u>and</u> - VL <100,000 copies /ml
3-12 years	<ul style="list-style-type: none"> Asymptomatic or mild symptoms (WHO Stage 3* or 4) <u>and</u> OR Asymptomatic or mild symptoms (WHO Stage 1 & 2) <u>and</u> CD4 <15% 	<ul style="list-style-type: none"> Asymptomatic or mild symptoms <u>and</u> <ul style="list-style-type: none"> - CD4 15-24 % <u>or</u> - VL >100,000 copies /ml 	<ul style="list-style-type: none"> Asymptomatic <u>and</u> <ul style="list-style-type: none"> - CD4 >25 % <u>and</u> - VL <100,000 copies /ml
>12 years	<ul style="list-style-type: none"> AIDS or significant HIV-related symptoms (WHO Stage 3* or 4) OR Asymptomatic or mild symptoms (WHO Stage 1 & 2) <u>and</u> CD4 <200 cells/mm³ or <15% 	<ul style="list-style-type: none"> Asymptomatic or mild symptoms <u>and</u> <ul style="list-style-type: none"> - CD4 201 >350 cells/mm³ <u>and</u> - VL <100,000 copies /ml 	<ul style="list-style-type: none"> Asymptomatic <u>and</u> <ul style="list-style-type: none"> - CD4 >350 cells/mm³ <u>and</u> - VL <100,000 copies /ml

* Except with TB, lymphoid interstitial pneumonitis (LIP), Oral Hairy leukoplakia (OHL) or thrombocytopenia. Starting antiretroviral in children with these conditions will depend on their CD4%

3.2.3 Issues and choice for initial antiretroviral therapy

a) Baseline resistance testing

Transmitted or primary drug resistance of HIV-1 has been reported in several countries with prevalence of genotypic resistance (among adult patients) ranging from 1% for major mutations in Malaysia^{155, Level 8} to 27.4% in San Francisco.^{156; Level 6} Trends in the prevalence of transmitted drug resistance over the last decade have been reported as increasing in several countries including Europe,^{157, Level 6} the United States^{158, Level 6} and the UK^{159, Level 6} while some others such as Australia^{160, Level 8}, France^{161, Level 8} and Amsterdam^{162, Level 8} have reported a decreasing trend. Transmitted resistance has been reported in both acute and chronic infections.

Among children with HIV infection, data from France and the US have indicated prevalence of 12-20%.^{163, Level 6; 164, Level 8}

These reports have largely come from countries with history of extensive use of antiretrovirals (including mono and dual therapy) prior to HAART becoming available.

There are very little data on primary resistance in Malaysia. The only study by Tee et al^{165, Level 8} from a small single centre cross sectional study among 100 recently diagnosed ARV naïve patients reported a prevalence of 1% (genotypic resistance) for major mutations conferring high level resistance.

There have been numerous reports of emergence of resistance among HIV-1 infected pregnant women receiving ARVs for treatment or for PMTCT. However there are few reports of transmitted resistance and its significance among infants and children.

Resistance to ZDV is usually seen after several months of partly suppressive therapy^{166, Level 9} and reported rates have ranged from 6.3% genotypic resistance in the 076 study^{167, Level 6} to 24% in the WITS study predominantly among treatment-experienced women.^{168, Level 6} Among mothers given ZDV there have been conflicting reports of the risk of transmission of resistant viral strains to the newborn ranging from none to 5 fold risk.^{168, Level 6 ; 169; Level 6} There have been reports of rapid development of resistance to 3TC in pregnant women especially related to duration of use but overall transmission to the newborn has been low.^{170, Level 8; 15, Level 6; 171, Level 8} Similarly the use of single dose NVP although associated with development of resistance in the mother, has not been associated with an increased risk of MTCT of resistant subtypes.

There have been very few reports evaluating the significance of transmitted drug resistance and the value of determining baseline resistance prior to initiating therapy and there have been no such studies in children and

infants. Some have found that time to viral suppression may be significantly longer in those with any resistance but an equivalent proportion did achieve suppression on longer follow-up,^{156, Level 6; 158, Level 6} while others found no effect of any baseline resistance on response to initial therapy.^{172, Level 6 ; 173, Level 6} One study found significant correlation between risk of failure and the number of mutations in the protease region.^{174, Level 6} There have been no direct studies among children to determine clinical significance of baseline resistance. A recent study from the UK suggests that individuals with transmitted resistance to multiple classes of drugs had significantly impaired response to first line ART.^{175, Level 6}

Considering the potential for increasing resistance with improved access to and use of ARVs among HIV infected individuals including infected pregnant women, WHO has issued the WHO Guidelines for Surveillance of HIV Drug Resistance in newly diagnosed and treatment-naïve HIV subjects 2003.

^{176, Level 9}

The estimates obtained from such surveillance will support planners and clinicians in selecting the appropriate regimens for prevention of vertical transmission and post exposure prophylaxis. The estimates may also aid in evaluating the initial standard regimens used in the country, and the success of expanded access treatment programmes. Finally, they will inform discussions on whether pre-treatment drug resistance testing or screening should be considered.

Recommendation for baseline resistance testing

There is insufficient evidence currently to support the need for baseline resistance testing prior to initiation of therapy for children and adolescents in Malaysia. **(Grade B)**

As transmitted drug resistance may become an increasing problem in Malaysia, it may be useful to undertake surveillance resistance testing among newly diagnosed patients.

b) Choice of drugs and regimen

Research into antiretroviral drugs and improved strategies for the treatment of HIV infection continue to evolve. There are few randomized phase III clinical trials of HAART among paediatric patients that provide direct comparison of different treatment regimens. Most of the data on ART are based on efficacy data from clinical trials in adults, pharmacokinetic data and safety data for phase I/II trials in children and nonrandomized open label studies in children.

The goal of ART is for effective and durable viral suppression in order to preserve or restore immune function and prevent HIV-related morbidity and mortality. The current standard of care for HIV infection is HAART which comprises **2 nucleoside reverse transcriptase inhibitors (NRTI) plus a 3rd active agent** (a non-nucleoside reverse transcriptase inhibitor [NNRTI] based or a protease inhibitor [PI] based). The clinical benefit of HIV therapy is largely dependent on improving or sustaining immune function and delaying disease progression over the long term.

The choice of drugs for children and adolescents is based on ability to achieve durable viral suppression, extent of paediatric/adolescent experience, acceptable toxicity profile, availability and palatability of paediatric formulations, dosing profile and drug interactions.

c). Infants & children

The following recommendations are adapted from the US Department of Health and Human Services Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection. ^{46, Level 9}

Recommendation for first-line antiretroviral therapy (ART) (infants & children)

The standard of care is HAART which comprises: **2 NRTI plus 3rd active agent** (NNRTI or PI - based).

NNRTI based:

≤3 years:

2 NRTIs + **Nevirapine**

≥3 years:

2 NRTIs + **Efavirenz**

PI Based:

2 NRTIs + **Lopinavir/ritonavir**

NRTI combinations:

Zidovudine **plus**

Lamivudine OR didanosine

Didanosine **plus**

Lamivudine

(Grade C)

Refer to Appendix 4 for details on individual ARV drugs

Notes:

- WHO encourages the use of fixed-dose combinations when formulations of assured quality and proven bioequivalence are available and offer operational advantages.
- Fixed-dose combinations of standard first-line ARV drugs that are suitable for children however are urgently required to facilitate treatment of HIV in children but are not yet available in Malaysia.

d) Adolescents

The following recommendations are adapted from the US Department of Health and Human Services Guidelines for the Use of Antiretroviral Agents in HIV-1 Infected Adults & Adolescents.^{177,Level 9} Adult guidelines for ART are considered appropriate for post pubertal adolescents.

Recommendation first-line antiretroviral drugs (adolescents)

The standard of care is HAART which comprises: 2 NRTI plus 3rd active agent (NNRTI based or PI based).

	Preferred Agent #	Alternative Agent*
NNRTI based :	Efavirenz	Nevirapine
PI Based:	Lopinavir/ ritonavir	Atazanavir

NRTI combinations

Preferred Combination*	Alternative Combination*
Zidovudine + Lamivudine (co- formulated)	Didanosine + Lamivudine

(Grade C)

Preferred agents # or combinations for use in treatment-naive patients are those where clinical trial data have demonstrated optimal efficacy and durability with acceptable tolerability and ease of use.

Alternative* components refer to those for which clinical trial data efficacy but also show disadvantages compared with preferred components in terms of antiviral activity, durability, tolerability, or ease of use.

Refer to Appendix 4 for details on individual ARV drugs

Efavirenz is not recommended for use in the 1st trimester of pregnancy or in sexually active women with child-bearing potential unless they are using effective contraception

Nevirapine should not be initiated in girls with CD4+ T cell count >250 cells/mm³ or in boys with CD4+ T cell count >400 cells/mm³ because of increased risk of symptomatic hepatic events in these patients.

e) Which HAART regimen to use?- NNRTI based or PI based

There have been very few direct comparative studies done - and none in children - to determine whether PI or NNRTI based regimen is more effective.

There are several factors in determining the optimum choice of regimen as first line therapy and these include effectiveness and durability of the regimen (virologic and immunologic), few adverse effects, tolerability, palatability with convenient dosing and possessing good future drug options.

De Luca et al,^{178, Level 6} in a cohort study determined that there was similar efficacy and tolerability for EFV- based compared with LPV/r-based first-line antiretroviral regimens. However, LPV/r was associated with higher rates of hypertriglyceridaemia. MacArthur et al,^{179, Level 1} reporting on the FIRST study (RCT of different regimens) in treatment naïve patients, found that clinical endpoints of AIDS defining event, death or CD4 decline to <200 were similar for both NNRTI and PI based regimens.

Virologic failure was less common with the NNRTI regimen with a more rapid decline in VL. Immunologic response (mean CD4 during 6 years follow-up) was similar in all treatment groups.

In a metaanalysis of direct and indirect data^{189, Level 1}, direct analysis found that NNRTI-based regimens were better than PI-based regimens for virologic suppression but both regimens did not differ in death or disease progression or withdrawal due to adverse events

Bartlett et al^{181, Level 1}, undertook a systematic analysis of studies of HAART in ARV naïve patients and demonstrated that NNRTI and boosted PI regimens provided the highest rates of virologic success but that future drug options were better with PI boosted regimens.

Choice of regimen should be individualized according to needs and patient factors; however there are numerous advantages of an NNRTI based regimen as first line and these include high virologic success, convenient dosing schedule, palatability and less metabolic adverse effects

Recommendation on choice of initial regimen

NNRTI-based regimens are the preferred choice as the first line HAART regimen for ARV naïve children unless specific patient needs or factors require a PI-based one. **(Grade C)**

f) Monitoring of HIV infected child on treatment

Careful monitoring is an essential component of effective ARV use. It permits assessment of treatment efficacy, early detection of adverse effects of therapy and ongoing reinforcement of adherence. The type and frequency of monitoring will be dependent on local resources. Monitoring is carried out by clinical and laboratory means.

g) Clinical Monitoring

This should include assessment of growth, development, psychological wellbeing, improvement in clinical status and absence of new or recurrent illnesses as well as evaluation of adherence and drug adverse effects.

It is known that weight and height growth of HIV infected children tend to lag behind that of uninfected children of similar age. HAART has been shown to improve the average weight gain of HIV infected children from subnormal to normal after 1 year of treatment and average height growth to nearly normal after 2 years of therapy.^{182, Level 2} Verweel et al^{183, Level 6} has also reported favourable response to height and weight parameters especially among children responding to HAART.

However, Lindsey et al,^{184, Level 6} report that despite viral suppression and improvement in immunologic status with HAART, there appears limited improvements in neurodevelopmental functioning in young children. Further studies are needed to further assess mental, neurological and psychological, physical, emotional and sexual maturation in children maintained on HAART.

h) Virologic monitoring

The aim of therapy is to suppress the plasma viral load to as low as possible and for as long as possible.

Definitions of response to therapy however are varied. In general, several studies have illustrated that most patients who respond and have durable suppression would have pVL decline by 1/10 or 1 log₁₀ from baseline after 8 weeks of therapy and viral suppression (pVL <50c/ml) by 24-32 weeks. Time to suppression may be longer in those with higher baseline pVL. The greater the rate of decline from baseline pVL, the higher the probability of durable suppression.^{185, Level 7;186, Level 8;187, Level 6 ;188, Level 6}

However not all patients can achieve suppression to below detectability. In such patients, a sustained pVL decline by 1.5-2 log₁₀ is considered adequate suppression.

i) Intermittent viremia

Among patients achieving viral suppression to undetectable (<50c/ml by ultrasensitive assay), there are a number who experience episodes of intermittent low level viremia or 'blips'. These are defined as single VL measurements of 50-200 c/mL. (sustained elevated results are considered virologic failure.) These episodes have been reported in 11-40% of patients on HAART. Several studies indicate that such intermittent viremia do not represent treatment failure although causes of these blips have yet to be determined.^{189, Level 6, 190, Level 6; 191, Level 6; 192, Level 6; 193, Level 6} There has also been no association with loss of adherence during these blips.^{194, Level 6;195, Level 6} One study demonstrated that 26% of these episodes were caused by

intercurrent infections.^{196, Level 6} A recent study by Nettles et al^{193, Level 6} suggested that these blips signify random biological and statistical variation around mean HIV-1 levels below 50 copies/mL rather than clinically significant elevations in viremia.

j) Immunologic Monitoring

The majority of patients (adults, children and adolescents) on HAART will show improvements in CD4 counts and percentages.^{197, Level 6; 140, Level 6; 198, Level 6; 199, Level 6} Among adults a plateau appears to be reached by 4 years^{197, Level 8} while the study on children^{198, Level 6} showed that improvements in CD4 continued throughout the second year follow-up.

There is little information on the expected rate of improvement among children. However, the younger the age and the lower the pre-treatment CD4 the greater the improvements. Thus an increase of 10% or more at 6 months of treatment was seen among children younger than 2 years of age where median time to achieve CD4 > 30% (pre-treatment CD < 25%) was less than 12 months in one study.^{198, Level 6} This study also demonstrated the mean CD4 increase at 6 months was 9% with inter-quartile ratio 4-13%.

Recommendation for monitoring

Clinical monitoring (pVL)

- Children on HAART should be evaluated clinically for adherence, drug adverse effects and improvements in weight, height and development. **(Grade C)**

Virologic monitoring

- Plasma viral load (pVL) should be monitored at week 8, week 12 and every 4-6 months thereafter or whenever there is a clinical event or significant decline in CD4+ T cells. **(Grade C)**
- Therapy is considered adequate if pVL declines by at least 1 log 10* by week eight and optimally to < 50copies/ml by week 24-32. In those not achieving viral suppression, a sustained decrease in HIV RNA copy number of 1.5 to 2.0 log₁₀ from baseline (if achieved RNA levels are low) may also be considered adequate. **(Grade C)**

Immunologic monitoring

- CD4 should be monitored 3-4 monthly for patients on HAART. **(Grade C)**
 - CD4 is expected to increase in the majority of children with increases in CD4% ranging from 5-10% at 6 months with continued rise through first 2-3 years of HAART.
 - Patients with discordant responses (no increase in CD4 despite viral load suppression, or improved CD4 but with continued high pVL) should be referred to paediatric infectious diseases specialist.

k) Adherence

Prospective cohort studies both in adults and children including adolescents have demonstrated the importance of high level of adherence to HAART of >90% for viral suppression and durability of response.^{201, Level 6 ;202 Level 9 ;203, Level 2}

These studies also demonstrate improved immunologic response with adherence to therapy.^{204, Level 6;205, Level 6 ; 199, Level 6; 206,Level 6}

Poor adherence is likely to result in subtherapeutic ARV levels with risk for virologic failure and emergence of drug resistance, thus not only affecting current regimen but also limiting future drug options.

Adherence is a major issue in paediatric treatment and there is evidence that adherence problems are common in children. In one study, 43% of people caring for a child receiving HAART reported at least one missed dose in the past week.^{207, Level 8} A number of factors could contribute to adherence problems: high pill/medication burden; refusal of young infants to take syrups due to unpleasant taste; unwillingness among caregivers to inform schools and care-centres that their child is infected, which could result in missing out on doses during the day; dietary restrictions; and toxic side effects of drugs.

l) Adherence assessment and monitoring

A comprehensive assessment for adherence should be carried out prior to initiation of therapy and should include social, behavioural, family and financial factors that may affect adherence by the child and family and to identify areas for intervention. A dialogue and partnership should be established providing information, obtaining agreement to treatment plan and to identify strategies for supporting adherence.^{46, Level 9}

m) Monitoring adherence

Adherence is difficult to assess accurately. There is as yet no definite tool to reliably and accurately assess adherence. Multiple methods are recommended.^{46,Level 9}

Methods to monitor adherence

- Viral load response
- Quantitative report of missed doses by caregivers, child or adolescent (focusing on recent missed doses during a 3-day or 1-week period)
- Descriptions of medication regimens
- Reports of barriers to administration of medication
- Targeted questions about stress, pill burden and daily routine
- Pharmacy refill data and pill counts
- Electronic devices (Medication Event Monitoring System)
- Home visits
- Hospitalization for supervision and monitoring
- Therapeutic drug monitoring

n) Improving & Supporting Adherence

Intensive follow-up and frequent assessment of adherence are important. Strategies to improve and support adherence should be identified and instituted. These include:

o) Regimen Strategies

- Choose the simplest regimen possible
- Choose the regimen that best conforms to daily routines of patient and family
- Choose the most palatable medicine possible
- Choose drugs with fewest side effects
- Simplify food requirements
- Avoid drug interactions
- Prescribe fixed-dose combinations with convenient once a day dosing if available

p) Child/ family related strategies

This emphasises patient / caregiver education about HIV-related disease, the need for adherence, providing tools such as written and visual materials, daily schedules, demonstrating use of syringes for liquid medications, pill boxes etc.

Behavioural tools can be used such as positive reinforcements with small incentives. For children who are persistently non-adherent and averse to taking medications, a gastrostomy tube may be considered. Home nursing and directly observed dosing are also possible options for the difficult cases.

q) Healthcare provider strategies

Fostering trusting relationship and open communication are important. Positive characteristics for healthcare providers include consistency, providing information, asking questions, technical expertise and commitment.

Recommendation for adherence

A comprehensive assessment for adherence should be carried out prior to initiation of therapy and should include social, behavioural, family and financial factors **(Grade C)**

Adherence should be supported by intensive follow-up and frequent assessment **(Grade C)**

Strategies to improve and support adherence include:

- Regimen strategies
- Child & family related strategies
- Healthcare provider strategies

Adherence must be monitored with the use of multiple methods as outlined above. **(Grade C)**

r) Immune Reconstitution Inflammatory Syndrome

Case reports and retrospective cohort studies have established immune reconstitution inflammatory syndrome (also known as immune reconstitution disease or immune restoration disease), as a significant problem among patients initiated on HAART. This condition is characterized by a paradoxical clinical worsening of a known condition or the appearance of a new condition after initiating ART and results from restored immunity to specific infectious or non-infectious antigens.

There is no generally accepted case definition due to diverse and still expanding clinical spectrum of this condition.

Proposed definition of IRIS includes the following: 208, Level 8

Receiving HAART

- Decrease in HIV-1 RNA level from baseline
- Increase in CD4+ cells from baseline (may lag HIV RNA decrease)

Clinical symptoms consistent with inflammatory process

Clinical course not consistent with:

- Expected course of previously diagnosed OI
- Expected course of newly diagnosed OI
- Drug toxicity

Possible infectious and non-infectious aetiologies of IRIS are summarized below: 209, Level 9

Infectious etiologies	Non-infectious etiologies
<ul style="list-style-type: none"> • <i>Mycobacterium tuberculosis</i> • <i>Mycobacterium avium complex</i> • Other mycobacteria • <i>Cytomegalovirus</i> • Herpes viruses • Herpes zoster virus • Herpes simplex virus • Herpes virus-associated Kaposi's sarcoma • <i>Cryptococcus neoformans</i> • <i>Pneumocystis jirovecii pneumonia</i> (PCP) • <i>Histoplasmosis capsulatum</i> • Toxoplasmosis • Hepatitis B virus • Hepatitis C virus • Progressive multifocal leukoencephalitis • Parvovirus B19 • <i>Strongyloides stercoralis</i> infection & other parasitic infections • Molluscum contagiosum & genital warts • Sinusitis • Folliculitis 	<ul style="list-style-type: none"> • Rheumatoid arthritis / Autoimmune • Systemic lupus erythematosus (SLE) • Graves disease, Autoimmune thyroid disease • Sarcoidosis & granulomatous reactions • Tattoo ink • AIDS-related lymphoma • Guillain-Barre' syndrome (GBS) • Interstitial lymphoid pneumonitis

The most common underlying infections associated with IRIS are mycobacteria, CMV, herpes simplex, varicella-zoster and hepatitis C.

The incidence of this condition has been reported as ranging from 15-45% among patients with a known underlying OI, majority occurring in the first 60 days, and 15-25% among all patients commencing HAART, majority in the first 3 months. ^{208, Level 8}

There are few data regarding IRIS among HIV infected children. In a prospective cohort study from Thailand, ^{210, Level 6} the incidence of IRIS was 19% and median time of onset 4 weeks after start of HAART (range, 2-31 weeks). The majority were caused by mycobacterial organisms, followed by varicella-zoster virus, herpes simplex virus and by *Cryptococcus neoformans*. 1 episode of Guillain-Barré syndrome was reported. Features included exacerbation (often with unusual manifestations) of a previously treated OI, or unmasking of a previously subclinical infection.

Risk factors for IRIS have not been clearly defined. Factors associated with this condition include lower baseline CD4 at initiation of therapy, higher baseline VL, a rise in CD4 after 90 days and a rapid fall in HIV RNA level during the first 3 months of therapy.

Pathogenesis of IRIS is not fully understood but suggested mechanisms include recovery of antigen specific immune response, response to high antigen burden, dysregulation of the immune response and disease susceptibility genes.

Most cases of IRIS resolve after a few weeks, however some can be severe with significant morbidity and occasional mortality. Treatment is directed to the specific aetiology by initiating or continuing specific therapy. A course of corticosteroids (prednisolone or methylprednisolone) for life threatening or unresponsive inflammatory responses may be necessary. ART should be continued but interruption may need to be considered in severe or unresponsive cases.

Recommendation for Immune Reconstitution Inflammatory Syndrome

Clinicians initiating HAART should remain vigilant for the occurrence of Immune Reconstitution Inflammatory Syndrome. **(Grade C)**

Treatment is directed towards the specific aetiology though steroids may need to be given in the severe cases. **(Grade C)**

Antiretroviral therapy should not be interrupted except in very severe or unresponsive cases. **(Grade C)**

3.2.4 Special issues for adolescents

Adolescents diagnosed with HIV infection have either been infected by horizontal transmission (sexual, injecting drug use) or are adolescent survivors of perinatal infection.

Differences have been described in the natural history and progression of HIV infection in adolescents when compared with adults. Although adolescents may be more susceptible to HIV infection, they have better thymic reserve, demonstrate less rapid disease progression and perhaps better immune reconstitution with treatment.^{211, Level 8}

Adolescence is a time of rapid physical, cognitive and social changes which may influence disease progression and ongoing care. Combined management with an adolescent physician is beneficial. Important elements of care include access to age-appropriate health care, mental health and substance abuse services, peer-to-peer support, sexual health, routine screening for sexually transmitted infections, risk reduction counselling and contraceptive counselling. Routine cervical screening should be included for adolescent girls and the possible use of HPV vaccines should be considered.

a) Antiretroviral therapy

Timing and choice of therapy have been outlined in the respective sections. Particular problems in the adolescent include possible extensive prior treatment for perinatally acquired disease, drug resistances and regimen failures and issues of sustaining adherence. In the PACTG 381 study,^{212, Level 8} only 24% of adolescents on HAART were completely adherent to their regimen.

b) Dosing

It is recommended that prepubescent adolescents (Tanner stage I or II) should be dosed according to paediatric guidelines while those in late puberty (Tanner stage V) should receive adult doses. *Refer Appendix 5 for details on Tanner staging*

c) Adolescent Females

Gynaecological care is an important part of care for the HIV infected female adolescent. Adolescents with HIV infection may be sexually active, therefore contraception and prevention of HIV transmission should be discussed, including the interaction of specific ARV drugs with hormonal contraceptive agents. The potential for pregnancy must be considered and this may alter choices of antiretroviral therapy. For example, efavirenz should be used with caution in females of child bearing age and should only be prescribed after intensive counselling and education about the potential effects on the fetus. PMTCT strategies and regimens during pregnancy are described in the relevant CPGs.

d) Barriers to ART Adherence

Barriers to adherence among adolescents include those related to development such as denial, mistrust, rebellion, concrete thinking and other issues such as fear of disclosure, poor understanding, chaotic lifestyle, substance abuse and lack of family support. Low self-esteem, depression and feelings of hopelessness are other common factors.

Efforts need to be focused on reinforcing adherence as described above and include pillboxes, timers, reminder systems, peer-to-peer adherence counselling. A lower pill burden, (e.g. co-formulated fixed dose combinations and drugs with daily dosing (e.g. Tenofovir) and regimens with minimal adverse effects all facilitate adherence.

e) Transition to Adult Care

Transition is facilitated if adult clinics are in the same facility, and where one or more providers work in both settings with similar multidisciplinary support.

3.2.5 Treatment failure

Most children can remain stable on HAART for many years. However, at some point, assessment of the regimen will become necessary. It must be noted however that the patient's best response will be to his/her first-line HAART regimen.

Treatment failure is defined as suboptimal response or a lack of sustained response to therapy. It can be defined as an inadequate virologic, immunologic, or clinical response to antiretroviral therapy. It usually begins with virological failure, followed by immunological failure and eventually clinical failure.^{213, Level 9}

Careful assessment is required to evaluate the aetiology of treatment failure and determine the appropriate management strategy. A change in ART may be considered in a number of different situations, including:

- Suboptimal virologic response to therapy or a sustained increase in viral load
- Suboptimal immune response to therapy or immunologic deterioration
- Suboptimal clinical response to therapy or clinical disease progression
- Significant drug intolerance or toxicity
- Significant and unmodifiable adherence issues.

DEFINITIONS OF TREATMENT FAILURE

Virological failure: ^{46, Level 9}

Incomplete viral response to therapy

- Reduction in plasma HIV RNA of less than $0.5 \log_{10}$ four weeks after initiation of therapy, and less than $1.0 \log_{10}$ reduction at eight weeks.*
- Failure to suppress plasma HIV RNA to undetectable levels within six months of treatment initiation*

Viral rebound

- Confirmed rebound viraemia after initial reduction to undetectable levels (i.e. repeated detection of HIV RNA >400 copies/mL.)*
- Confirmed $>0.5 \log_{10}$ (greater than 3-fold) increase in HIV RNA copy number for children age ≥ 2 years or $>0.7 \log_{10}$ (greater than 5-fold) increase for children age < 2 years from the nadir achieved.
(For those who demonstrated an initial HIV RNA response but still had low levels of detectable HIV RNA)

Immunological failure: ^{213, Level 9}

- Non-correction or reappearance of low CD4 percentage in children (generally 20%, but could be lower in older children) or CD4 count in adolescents

Clinical failure: ^{154, Level 9}

- Presence of clinical symptoms in a child on therapy that are suggestive of a more severe clinical stage
- Development of a new or recurrent stage 3 or 4 clinical event in a child who had been on treatment for at least 24 weeks.

* Children with higher HIV RNA levels at initiation of therapy may take longer to fully suppress viral replication. The initial HIV RNA of the child at the start of therapy and the level achieved with therapy should be considered when contemplating potential drug changes.

For example, an immediate change in therapy may not be warranted if there is a sustained 1.5 to $2.0 \log_{10}$ fall in HIV RNA copy number, even if RNA remains detectable at low levels ^{46, Level 9}.

Continued observation with more frequent evaluation of HIV RNA levels should be considered if the HIV RNA increase is limited (e.g. $< 5,000$ copies/mL).

a) Causes of treatment failure include:

- Poor adherence ^{213, Level 6}
- Inadequate drug levels due to pharmacokinetic issues ^{213, Level 6}
- Inadequate potency of the drugs chosen ^{213, Level 9}
- Baseline characteristics of the child prior to initiation of a new therapeutic regimen, including viral load and CD4 cell percentage or count; high levels of immune cell activation; and the presence of drug resistance ^{46, Level 9}
- Absence of suitable paediatric formulations

b) Changing ART**When to change**

A diagnosis of treatment failure should only be made after the patient has had a reasonable trial of treatment for at least 24 weeks. Adherence to therapy should be assessed and considered prior to switching to second-line regimen. Clinicians should evaluate both clinical and immunological findings together before deciding on switching therapy. ^{154, Level 9}

Recommendation for switching therapy to second line regimen for treatment failure (after 24 weeks of optimum treatment). ^{154, Level 9}

WHO clinical stage	Management options
Stage 1 and stage 2	Consider switching regimen only if two or more CD4 values below age-related threshold for severe immunodeficiency are found
Stage 3	Switching regimen is recommended if CD4 at or below age-related threshold for severe immunodeficiency
Stage 4	Switch regimen regardless of CD4

Choice of ARV

The new second line regimen should preferably include at least 3 new drugs one or more of them from a new class in order to increase the likelihood of treatment success and minimize the risk of cross-resistance. ^{154, Level 9}

Recommended second line regimen in infants and children in the event of treatment failure of first line regimen (Grade C)

First line regimen at failure	Preferred second line regimen
2 NRTI + 1 NNRTI	2 new NRTI's plus PI
2NRTIs + PI	2 new NRTI's plus NNRTI
	2 new NRTI's plus alternative PI (boosted PI)
	1 new NRTI plus NNRTI plus alternative PI (boosted PI)

Notes:

- It is not recommended to introduce ZDV after use of d4T or vice versa
- EFV is not currently recommended for children <3 years of age, and should be avoided in post-pubertal adolescent girls who are either in first trimester of pregnancy or are sexually active and not using adequate contraception.
- Alternative NRTIs are Abacavir/ Tenofovir
- Alternative PIs are Atazanvir, Ritonavir, Saquinavir, Nelfinavir

Recommendation for second line therapy

Patient must be given an adequate trial of treatment for at least 24 weeks before treatment failure is considered. **(Grade C)**

Adherence to therapy should be assessed prior to switching to second-line regimen. **(Grade C)**

Clinicians must evaluate both clinical staging and CD4 value before considering change of treatment to second line therapy. **(Grade C)**

Before switching to second line therapy, consultation with Paediatric Infectious Disease Specialist is recommended. **(Grade C)**

Salvage therapy and multiple antiretroviral therapy failure

Salvage treatment is treatment reserved for children who have already received and failed two or more regimens.^{213, Level 9}

Salvage combinations may include more than three drugs. Combinations of four or five drugs are possible (Mega-HAART). Unfortunately, Mega-HAART regimens have a high risk of poor tolerability, cumulative toxicity and adherence problems. Salvage regimens should contain at least one other and ideally two or three new active drugs to achieve the best chance of success. It is unwise to add a single new drug to a failing regimen.^{213, Level 9}

As there is limited evidence with regards to salvage therapy, no definite recommendations can be provided and these patients should be referred to the Paediatric Infectious Diseases Specialist.

Recommendation for salvage therapy

- Salvage treatment is treatment reserved for children who have already received and failed two or more regimens. Refer to Paediatric Infectious Disease specialist for further management. **(Grade C)**

Resistance testing or genotypic testing

The prevalence of resistance in children who had failed HAART and had virological failure is high ranging from 71% to 90%. There is a close relationship between therapeutic failure and genotypic resistance.^{214, Level 6 ; 215, Level 6}

Ideally genotypic resistance assays should be carried out in children failing therapy. These assays should be obtained when the patient is still on the failing regimen or within 4 weeks of discontinuation of the regimen and while the patient has a pVL of > 1000c/ml. If resistance testing is not carried out, a sample should be stored for subsequent analysis.

Some reports in children have shown genotypic resistance testing to be useful for guiding therapy particularly for children with extensive ARV experience.

^{46, Level 9}

Recommendation for resistance testing

ARV drug resistance testing* is recommended prior to changing therapy for treatment failure. **(Grade B)**

Resistance assays* should be obtained when the patient is still on the failing regimen or within 4 weeks of discontinuation of the regimen and while the patient has a pVL of > 1000c/ml. **(Grade B)**

* This test is currently not available for clinical purposes

When to stop ART

If children have failed multiple ART regimens and no further suitable ARVs are available, stopping ART and keeping them comfortable with symptom-based palliative care may have to be considered.^{154 Level 9}

These children may experience undue suffering from psychological problems, pain, diarrhoea, cough, shortness of breath, nausea, weakness, fatigue, fever and confusion. Palliative care aims at relieving pain, treating the above symptoms, providing psychological support for patient and family and helping them with preparation for death. (Refer to palliative care guidelines).^{216, Level 9 ; 217, Level 9}

3.2.6 Management of medication toxicity or intolerance

- If a child has severe or life-threatening toxicity, all components of the drug regimen should be stopped immediately. Once the symptoms of toxicity have resolved, antiretroviral therapy should be resumed with substitution of another antiretroviral drug for the responsible drug.
- Children with moderate medication toxicity should continue on antiretroviral therapy when possible while an assessment is done to identify and substitute for the offending agent.
- Children with mild toxicity can be treated symptomatically, and do not require drug discontinuation or change in drug therapy.
- When changing therapy because of toxicity or intolerance to a specific drug, changing a single drug in a multi-drug regimen is permissible; if possible, an agent with a different toxicity and side effect profile should be chosen. ^{46, Level 9}

3.2.7 Short-term therapy interruption

- Short-term interruptions of ARV drugs may be indicated in some situations such as serious treatment-related toxicity, acute illness or surgery.
- When short-term interruptions are required, then all antiretroviral drugs should be stopped at the same time, if these medications have similar half-lives.
- However when agents with long half-lives are used (especially the NNRTIs EFV and NVP) cessation of all ARVs simultaneously could result in functional monotherapy with risk of resistance to these agents. To prevent functional monotherapy, some experts recommend stopping the NNRTI component first and continuing the other ARV drugs for a period of time (the optimum duration still not known - WHO recommends a one-week tail of the NRTI drugs).
- In case of serious or life-threatening ARV therapy toxicity, all drugs should be stopped immediately.

4. COMMON OPPORTUNISTIC INFECTIONS (OI) AND COMPLICATIONS IN HIV INFECTED CHILDREN

4.1 PATTERN OF OPPORTUNISTIC INFECTIONS

The pattern of opportunistic infections (OI) among HIV infected children differs from that of adults. Many OI in adults are secondary to reactivation of previously acquired opportunistic pathogens, which were acquired when host immunity was intact. However, OI among HIV infected children more often reflect primary infection with the pathogen. In addition, among children with perinatal HIV infection, the primary infection with the opportunistic pathogen is occurring after HIV infection is established when the child's immune system might already be compromised.^{218, Level 9}

In general children with HIV infection are at increased risk of bacterial infections such as diarrhoeal disease and pneumonia. Common bacterial pathogens include *Pneumococcus*, *Staphylococcus*, *non-typhi Salmonellae* and other gram-negative organisms.^{219, Level 5}

The data for OI locally and globally are limited. A large multicentre prospective cohort study from the USA (2767 enrolled) has shown the incidence of OI has decreased in the HAART era.^{219, Level 5} The most common OI in this study was bacterial pneumonia with a Cumulative Incident Rate (CIR) of 2.15 per 100 person-years(py). It accounted for 22.2% of all OI. The other OIs found were Herpes zoster/varicella (CIR 1.55/py), dermatophyte infections (IR 0.88/py) and oral candidiasis (CIR 0.93/py) Similar findings were seen in another prospective cohort study.^{225, Level 5}

In descriptive studies from developing and less developed countries bacterial pneumonia and sepsis are also the most common OIs. However unlike data from the USA, PCP and pulmonary tuberculosis seem to be more common.^{221, Level 8; 222, Level 8} In Thailand, disseminated infection with the fungus *Penicillium marneffeii* is one of the most common opportunistic infections.^{223, Level 8}

4.2 PREVENTING OPPORTUNISTIC INFECTIONS

In a large RCT study (African setting) co-trimoxazole prophylaxis significantly reduced all-causes mortality by 43% in asymptomatic and symptomatic HIV infected children (aged >1 year).^{128, Level 2} A Cochrane review used this single study to recommend that TMP/SMX prophylaxis be used to decrease mortality and morbidity among HIV infected children.^{224, Level 1} This benefit was seen across a large range of CD4 count thus concluding that the benefit could be due to a reduction in PCP and non PCP. In this same study Chintu et al^{128, Level 2} also showed a 23% reduction in hospital admission.

WHO recommends that TMP/SMX be offered to asymptomatic (WHO Stage 1) children with CD4 <25% (<5 years of age), CD4 < 200/ μ l (> 5 years of age) and all symptomatic (WHO Stage 2, 3 or 4) children older than 12 months, regardless of CD4 percentage or count.^{129, Level 9}

Commencing a patient on TMP/SMX prophylaxis also provides the opportunity to assess likely adherence when HAART is eventually commenced.

4.2 (a) Dosage and regimens of co-trimoxazole for OI prophylaxis

Various dosages have been used for the prophylaxis, these are usually based on weight, surface area or age. WHO Expert Consultation on TMP/SMX prophylaxis in HIV infection report dated May 2005 recommends daily doses according to age categories.^{129, Level 9}

The Zambian RCT also used age categories for dosing (40mg TMP/200mg SMX daily for children less than 5 years and 80mg TMP/400mg SMX for more than 5 years of age).^{128, Level 2} A recommendation for dosage extrapolated from these studies is 3-6mg/kg TMP/15-18mg/kg SMX daily.

4.2 (b) Safety of PCP prophylaxis medications

In a large RCT among children there was no significant difference in the incidence of adverse effects between placebo and co-trimoxazole.^{128, Level 8} Madhi reported that skin rash was the main side effect (2.8%) in infants given co-trimoxazole.^{124, Level 8} Other possible side effects include bone marrow toxicity and hepatotoxicity.^{129, Level 9} These side effects may be monitored on a clinical basis, using a symptomatic approach.^{129, Level 9} Dapsone and aerosolized pentamidine are alternatives for a child who is intolerant to co-trimoxazole. In a randomized, multicenter trial comparing different regimens of dapsone, none of the children in the daily 2 mg/kg regimen developed PCP.^{131, Level 9} The recommended dose of aerosolized pentamidine in children aged 5 years and older is 300 mg once monthly.^{226, Level 9}

Recommendation on prophylaxis using co-trimoxazole

Prophylaxis for an HIV infected child should be guided by age, WHO staging and CD4 % (**Grade C**)

Cotrimoxazole dosage -

- 4mg TMP/20mg SMX /kg daily (**Grade B**)

OR

- 150 mg TMP/ 750 SMX mg/m²/day divided twice daily for 3 days per week (**Grade B**)

Alternative to co-trimoxazole

Dapsone (2mg /kg daily) (**Grade B**)

OR

Aerosolized pentamidine

- Children 5 years of age and older - 300 mg once every four weeks (**Grade C**)
- Children less than 5 years of age- either 120 mg once monthly or 60 mg every 2 weeks, after a 4 week period of induction therapy at 60 mg/week (**Grade B**)

Please refer to Appendix 6 for details of investigations for opportunistic infections.

5. NON INFECTIOUS COMPLICATIONS OF HIV

In addition to secondary infections, health care personnel managing HIV infected children should be vigilant of the non-infectious complications of HIV.

5.1 MALIGNANCY

There is an increased incidence of malignant disease in children with vertically acquired HIV infection.^{227, Level 8} However, the number of children with HIV infection who develop a malignancy is poorly defined. The tumours seen in HIV infected children are somewhat different than those in adults and the spectrum appears to be age-dependent. Non-Hodgkin lymphoma is the most common cancer in HIV infected children. Other significant malignancies occurring in children with AIDS are Kaposi sarcoma, Hodgkin disease, primary brain lymphomas and leiomyosarcoma.^{227, Level 8; 228, Level 8}

5.2 NEUROLOGIC COMPLICATIONS

Non-infectious neurologic manifestations of AIDS were reported to occur among 10% of patients less than 18 years of age.^{229, Level 8} They presented with a variety of neurological manifestations including focal motor signs, altered tonus, retarded neurodevelopment, cognitive disturbances, intractable headache, seizures, and coma. The study showed that the mean age of presentation amongst vertically transmitted children was 5.8 years (range, 2-11 years).

5.3 HIV-ASSOCIATED NEPHROPATHY

Strauss reported that 8% of 155 children with AIDS developed HIV-associated nephropathy (HIVAN) They presented with persistent proteinuria, azotemia, haematuria, renal tubular acidosis, and end-stage renal disease.^{230, Level 8} Focal segmental glomerulosclerosis (FSGS) is the predominant glomerular lesion in HIVAN. Other reported glomerular lesions in patients with HIV include IgA nephropathy and cryoglobulinemia.^{230, Level 8 ;231, Level 8}

5.4 CARDIAC COMPLICATIONS

HIV infected children developed cardiac complications ranging from clinically silent lesions to fatal disease.^{232, Level 8} The reported complications include left ventricular dysfunction, cardiomegaly and pericardial effusion. Cardiac dysfunction is independent risk factor for mortality in HIV infected children.^{233, Level 8}

5.5 LYMPHOCYTIC INTERSTITIAL PNEUMONITIS (LIP)

A study of HIV infected children with chronic lung disease showed that almost 60% of the patients had lymphocytic interstitial pneumonitis.^{234, Level 8} Up to a third of all HIV infected children develop LIP and this usually presents in the 2nd or 3rd year of life. Affected children tend to have a better prognosis than children without LIP but secondary bacterial pneumonias and eventual bronchiectasis are common. LIP is classified as non-AIDS and Stage 3 (WHO Classification).

Clinical features that are often associated with LIP include generalised and symmetrical lymphadenopathy, bilateral chronic non-tender parotid swelling, digital clubbing and hepatomegaly. Typical radiographic findings are diffuse bilateral reticulonodular infiltrates. ART improves symptoms and radiographic appearances of LIP and resolution of LIP has been reported among adults receiving HAART^{235, Level 9; 236, Level 9}

6. OTHER ISSUES

6.1 DISCLOSURE

Perinataly acquired HIV infection has become a chronic illness due to advances in medical treatment. As an increasing number of children infected with HIV live to older ages, the question of disclosure of the diagnosis (to the child and others) becomes more crucial. This maybe particularly challenging when children reach school going age. Their psychosocial needs are also changing to more closely resemble the needs of the chronically ill individual, rather than the terminally ill. Disclosure of the child's HIV diagnosis is controversial and an emotionally laden issue. The importance of disclosure relates directly to medication adherence, treatment compliance, child's developing autonomy and avoids potential transmission to sexual partners.

6.1.1 Disclosure rates

In a Thai study involving primary caregivers of 96 HIV infected children aged 5 years and older; disclosure was made to only one in 5 HIV infected children. Common reasons for non-disclosure were concerns that the child was too young, that the child might be psychologically harmed, and that the child could not keep the secret.^{237, Level 8} The fear of the negative impact on the family due to the stigma associated with HIV infection or 'AIDS' is also a reason for families to avoid disclosure.^{244, Level 9; 245, Level 9} However, Battles et al reported that disclosure was found to be positively related to social support, self-competence, and decreased problem behavior except in the case of public disclosure.^{240, Level 9}

6.1.2 Disclosure and adherence

Adherence to daily drug regimens is an important aspect of management. Among the factors that can influence adherence is the disclosure of diagnosis to the child. Using in-depth interviews of 42 HIV infected children on treatment and their care givers in a HIV clinic (Uganda) it was noted that complete disclosure by caregivers to children & strong parental relationships were related to good adherence.^{241, Level 8} In Puerto Rico 70% HIV positive youth had feelings of normalcy 6 months post-disclosure and most also improved their adherence to therapy after disclosure. Eighty-five percent of youth and 97% of caregivers considered disclosure a positive event for themselves and their families.^{242, Level 8}

6.1.3 When and how

In a Thai cross-sectional study conducted among 103 care givers of HIV infected children aged >6 years who were receiving HAART, disclosure rates were 30% and the average age for disclosure was 9.2 years. Almost all (88.7%) care givers agreed that they should tell the children their diagnosis in the future but half needed health-care providers to help them at the event.^{243, Level 8} The frequency of disclosure increased with age - 9% by 5 years; 18% by 6 years; 20% by 7 years; 33% by 8 years; 39% by 9 years; 48% by 10 years; 50% by 11 years; 83% by 12-13 years; 91% by 14-15y; 100% greater than 15 years.^{244, Level 9}

In a cross-sectional study of 51 HIV infected children (based on medical records, parent interviews, and child assessments) the probability of earlier age of disclosure is associated with higher child IQ and more family expressiveness.^{245, Level 7} Disclosure should take into consideration the child's age, maturity, complexity of family dynamics and clinical status. Furthermore, while parents may be making requests for non-disclosure based on what they believe is best for their child, health care professional also have a responsibility to continuously make an independent assessment of a child's readiness for disclosure.^{246, Level 9}

Recommendation for disclosure

Health care professionals need to educate and counsel care givers on the importance of disclosure of diagnosis to the infected child. This counselling may need to be repeated. **(Grade C)**

Disclosure of the diagnosis needs to be individualized, planned and offered in stages to the child and family. **(Grade C)**

This process should take into consideration the child's cognitive ability, developmental stage, clinical status, social circumstances, knowledge and coping capacity. **(Grade C)**

Disclosure of HIV infection status should be encouraged by school-going age (7-10 years) and should be achieved by 15 years of age. **(Grade C)**

Health care professionals need to facilitate the process of disclosure and when required play the lead role in the disclosure process. **(Grade C)**

Health care professional needs to continuously assess and educate the child after disclosure. **(Grade C)**

6.1.4 School and Disclosure

A healthy school environment reduces the risk of HIV transmission, accommodates students and staff infected with or affected by HIV, and maintains the confidentiality of students and staff living with HIV.

There is a need for school policies that address issues raised by HIV infection including disclosure, confidentiality, infection control and first aid practices and so on, which can provide essential guidance to educators, reassurance to families, students, and school staff members, and support for people with the virus.

An HIV infected child's parent or guardian is not obliged to disclose the student's HIV status to school personnel. Realistically in a need to know situation, no more than two staff need to know if a pupil is affected or infected by HIV. One would normally be the head teacher and the other a designated staff member, ideally chosen by the pupil and parent, who can oversee the child's education, care and well-being and provide supportive counselling when necessary. The majority of infected children spend their school career healthy, but they may need time off for medical appointments and may occasionally have periods in hospital. The role of the head teacher will be to support the designated staff member, to discuss any issues with him or her and to instigate any discussion between parents and the school on issues that arise concerning the pupil's education or well-being.^{247, Level 9}

6.2 AGE APPROPRIATE EDUCATIONAL & LIFESTYLE ADVICE FOR CHILDREN AND ADOLESCENTS

HIV infected children, adolescents and their caregivers should be given appropriate advice regarding behaviour and lifestyle to minimize the risk of HIV transmission. The advice provided must be appropriate to the age and maturity of the child.

The risk of a young child infecting others is extremely small. Although HIV has been isolated in the saliva, tears, urine and faeces, there is no evidence that HIV can be acquired through casual contact with these sources.^{246, Level 9} Families and caregivers should be assured that sharing of household utensils, linen, clothes, personal hygiene products and close daily interactions (including kissing) are safe and do not result in the transmission of HIV.

Having an infected child in a day-care centre or school poses no risk to staff or other children. No case has ever been recorded of HIV transmission from child to child by playing, fighting or any other normal childhood interaction. Although biting poses a theoretical risk of transmission, the risk is believed to be extremely low.^{249, Level 9 ; 250, Level 9} If an infected child has a cut or graze, this should be dealt with in the normal manner following first aid procedures and standard hygiene practices. Schools should be assisted to develop a norm in which universal or standard precautions for infection control are routinely employed by staff and students (see Appendix 9 for additional resources).

As the child grows up into adolescence, several pertinent issues must be addressed (see following table). Disclosure of the diagnosis is important and frank and open discussion is vital so he/she can participate in decisions regarding treatments, care and prevention of transmission to others. Specific issues regarding lifestyle or behaviour that potentially could transmit HIV, especially sexual activity and substance abuse must be addressed. These prevention messages should be regularly provided to HIV infected adolescents at every opportunity.

Points to emphasize during counselling of adolescents with HIV infection:*251, Level 9; 252, Level 9

- The need for safer behaviours to protect their own health and the health of others.
- Providing adequate and accurate information regarding factors that influence HIV transmission and methods that can reduce the risk, emphasizing that the most effective methods for preventing transmission are those that protect non-infected persons against exposure to HIV (e.g. sexual abstinence; if sexually active, practising safe sex by using condoms, no needle-sharing).
- Identifying and correcting misconceptions regarding HIV transmission and methods for reducing risk for transmission. e.g. use of HAART does not eliminate the risk of transmitting HIV to others.
- Addressing the consequences of involvement in substance abuse.
- Referring to appropriate harm reduction treatment and drug rehabilitation programmes (e.g. methadone replacement program) for those involved in injecting drug use.

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WHO CLINICAL STAGING OF HIV/AIDS FOR CHILDREN WITH CONFIRMED HIV INFECTION.

Source : World Health Organisation, WHO Definitions of HIV Surveillance and Revised Clinical Staging and Immunological Classification of HIV related disease in Adults and Children 2007

Clinical Stage 1

Asymptomatic
Persistent generalized lymphadenopathy

Clinical stage 2

Unexplained persistent hepatosplenomegaly
Papular pruritic eruptions
Fungal nail infection
Angular cheilitis
Lineal gingival erythema
Extensive wart virus infection
Extensive molluscum contagiosum
Recurrent oral ulcerations
Unexplained persistent parotid enlargement
Herpes zoster
Recurrent or chronic upper respiratory tract infections (otitis media, otorrhoea, sinusitis or tonsillitis)

Clinical stage 3

Unexplainedⁱ moderate malnutrition or wasting not adequately responding to standard therapy
Unexplained persistent diarrhoea (14 days or more)
Unexplained persistent fever (above 37.5°C intermittent or constant for longer than one month)
Persistent oral candidiasis (after first 6- 8 weeks of life)
Oral hairy leukoplakia
Acute necrotizing ulceration gingivitis or periodontitis
Lymph node tuberculosis
Pulmonary tuberculosis
Severe recurrent bacterial pneumonia
Symptomatic lymphoid interstitial pneumonitis
Chronic HIV-associated lung disease including bronchiectasis
Unexplained anaemia (<8g/dl), neutropaenia (<0.5 x 10⁹ per litre) and or chronic thrombocytopenia (<50 x 10⁹ per litre)

i. Unexplained refers to where the condition is not explained by other causes

Clinical stage 4ⁱⁱ

Unexplained severe wasting, stunting or severe malnutrition not responding to standard therapy
Pneumocystis pneumonia
Recurrent severe bacterial infections (such as empyema, pyomyositis, bone or joint infection or meningitis but excluding pneumonia)
Chronic herpes simplex infection (orolabial or cutaneous of more than one month's duration or visceral at any site)
Oesophageal candidiasis (or candidiasis of trachea, bronchi or lungs)
Extrapulmonary tuberculosis
Kaposi sarcoma
Cytomegalovirus infection: retinitis or cytomegalovirus infection affecting another organ, with onset at age older than one month
Central nervous system toxoplasmosis (after one month of life)
Extrapulmonary cryptococcosis (including meningitis)
HIV encephalopathy
Disseminated endemic mycosis (coccidiomycosis or histoplasmosis)
Disseminated non-tuberculous mycobacterial infection
Chronic cryptosporidiosis (with diarrhea)
Chronic isosporiasis
Cerebral or B-cell non-Hodgkin lymphoma
Progressive multifocal leukoencephalopathy
Symptomatic HIV-associated nephropathy or HIV-associated cardiomyopathy

ii. Some additional specific conditions can also be included in regional classifications (such as reactivation of American trypanosomiasis [meningoencephalitis and/or myocarditis] in the WHO Region of the Americas, disseminated penicilliosis in Asia and HIV-associated rectovaginal fistula in Africa).

WHO CLINICAL STAGING /AIDS FOR ADULTS AND ADOLESCENTS WITH CONFIRMED HIV INFECTION

Source : World Health Organisation, WHO Definitions of HIV Surveillance and Revised Clinical Staging and Immunological Classification of HIV related disease in Adults and Children 2007

Clinical stage 1
Asymptomatic Persistent generalized lymphadenopathy
Clinical stage 2
Moderate unexplained weight loss (<10% of presumed or measured body weight) ⁱ Recurrent respiratory tract infections sinusitis, tonsillitis, otitis media and pharyngitis) Herpes zoster Angular cheilitis Recurrent oral ulceration Papular pruritic eruptions Seborrhoeic dermatitis Fungal nail infections
Clinical stage 3
Unexplained ⁱⁱ severe weight loss (>10% of presumed or measured body weight) Unexplained chronic diarrhoea for longer than one month Unexplained persistent fever (above 37.6°C intermittent or constant, for longer than one month) Persistent oral candidiasis Oral hairy leukoplakia Pulmonary TB (current) Severe bacterial infections (such as pneumonia, empyema, pyomyositis, bone or joint infection, meningitis or bacteraemia) Acute necrotizing ulcerative stomatitis, gingivitis or periodontitis Unexplained anaemia (<8 g/dl), neutropaenia (<0.5 × 10 ⁹ per litre) or chronic thrombocytopenia (<50 × 10 ⁹ per litre)

i. Assessment of body weight in pregnant woman needs to consider the expected weight gain of pregnancy.

ii. Unexplained refers to where the condition is not explained by other causes

WHO CLINICAL STAGING /AIDS FOR ADULTS AND ADOLESCENTS WITH CONFIRMED HIV INFECTION

Clinical stage 4 ⁱⁱⁱ
HIV wasting syndrome Pneumocystis pneumonia Recurrent severe bacterial pneumonia Chronic herpes simplex infection (orolabial, genital or anorectal of more than one month's duration or visceral at any site) Oesophageal candidiasis (or candidiasis of trachea, bronchi or lungs) Extrapulmonary tuberculosis Kaposi's sarcoma Cytomegalovirus infection (retinitis or infection of other organs) Central nervous system toxoplasmosis HIV encephalopathy Extrapulmonary cryptococcosis including meningitis Disseminated non-tuberculous mycobacterial infection Progressive multifocal leukoencephalopathy Chronic cryptosporidiosis (with diarrhea) Chronic isosporiasis Disseminated mycosis (coccidiomycosis or histoplasmosis) Recurrent non-typhoidal Salmonella bacteraemia Lymphoma (cerebral or B-cell non-Hodgkin) or other solid HIV-associated tumours Invasive cervical carcinoma Atypical disseminated leishmaniasis Symptomatic HIV-associated nephropathy or symptomatic HIV-associated cardiomyopathy

iii. Some additional specific conditions can also be included in regional classification (such as reactivation of American trypanosomiasis [meningoenkephalitis and /or myocarditis] in the WHO Region of America and disseminated penicilliosis in Asia)

IMMUNOLOGICAL CLASSIFICATION

Table : 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%

- CD4 (absolute count or %) is the recommended measurement to assess immune deficiency.
- The CD4% /count should be used in conjunction with clinical assessment; however, CD4% /count allows early detection of worsening of HIV disease, as the CD4% / count usually falls before clinical progression takes place.
- CD4 monitoring can aid in the decision to initiate ART or switch to another ARV drug.
- Younger children normally have higher CD4 counts than older children and adults.
- CD4% is the preferred measurement in children <5 years old, as it varies less in them than in older children.
- At >5 years of age, either CD4% or absolute CD4 count can be used. (Recent studies in adults suggest that CD4% may predict disease progression independent of absolute CD4 (Moore et al 2006, Pirzada et al 2006, Hulgan et al 2007 Level 6)
- The threshold CD4 levels for severe immunodeficiency in children >1 year of age correspond with a 12-month mortality risk of ≤5%. In children <1 year of age, especially those <6 months, the CD4% / count is less predictive of mortality and there is a high risk for death even if the CD4% is high.

ANTIRETROVIRAL DRUGS

Nucleoside Analogue Reverse Transcriptase Inhibitors

DRUG	DOSAGE	ADVERSE REACTIONS	DRUG INTERACTIONS	SPECIAL INSTRUCTIONS
Abacavir (ABC) ZIAGEN Preparations: Pediatric oral solution 20mg/ml Tablets: 300mg	<u>Pediatric Dose:</u> 3 months to 16 years of age; 8 mg/kg twice daily; (maximum dose 300 mg twice daily) <u>Adolescent/Adult Dose:</u> 300 mg orally twice daily or 600 mg once daily	More common: Nausea, vomiting, fever, headache, diarrhea, rash and anorexia Less common (more severe): Hypersensitivity reaction: symptoms include fever, malaise, fatigue, nausea, vomiting, diarrhea, and abdominal pain or respiratory symptoms such as shortness of breath, STEVENS-JOHNSON SYNDROME (some fatal cases) Lactic acidosis, severe hepatomegaly with steatosis Rare: Increased liver enzymes, elevated blood glucose and elevated triglycerides	Combination with Ribavirin has resulted in fatal or nonfatal lactic acidosis therefore coadministration of these two agents should only occur if the potential benefit outweighs the potential risks	May take with or without food. Store oral solution at room temperature. Abacavir should NEVER be re-started following a hypersensitivity reaction or if hypersensitivity cannot be ruled out BECAUSE HYPOTENSION AND DEATH HAVE OCCURRED UPON RECHALLENGE.
Didanosine (ddl) VIDEX Preparations: Pediatric powder for oral solution, 2G (must be mixed with antacid): 10mg/ml Chewable tablets with buffers: 25mg, 100mg Enteric Coated (EC) Delayed Release Capsule: 125mg, 200mg, 250mg, 400mg	<u>Pediatric Dose:</u> 2 weeks to 8 months of age: 100 mg/m ² q12H 8 months of age and older, 120 mg/m ² twice daily, clinical studies have used a pediatric dose range of 90 - 150mg/m ² q12H <u>Adolescent/ Adult Dose:</u> Tablets < 60kg: 125 mg twice daily or 250 mg once daily; > 60kg: 200 mg twice daily or 400 mg once daily (twice daily dosing is preferred, it provides better therapeutic response than once daily dosing) Delayed-release capsules < 60kg: 250 mg once daily; > 60kg: 400 mg once daily	More common: Diarrhea, abdominal pain, nausea, vomiting Less common (more severe): Pancreatitis(dose related - less in children), peripheral neuropathy (dose related), electrolyte abnormalities, hyperuricemia, severe hepatomegaly with steatosis, (some fatal cases), increased liver enzymes, Serious in pediatric age groups: Diabetes mellitus, retinal or optic nerve changes (rare)	Possible decrease in absorption of ketoconazole, itraconazole; administer at least 2 hrs before or 2 hrs after ddl. Ganciclovir may increase peak levels of ddl and predispose to toxicity. Administration with protease inhibitors: Indinavir should be administered at least one hour apart from ddl on an empty stomach. Ritonavir should be administered at least 2 hours apart from ddl. Combination with Hydroxyurea is not recommended, appears to increase the risk of pancreatitis Combination of d4T and ddl is not recommended because of overlapping toxicities.	The dosing interval (BID) should be every 12 hours. Decreased dosage should be used for patients with impaired renal function. Ddl formulation contains buffering agents or antacids. Food decreases absorption; administer ddl on an empty stomach (30 minutes before or 2 hrs after a meal). EC Capsules should be swallowed intact (not chewed). For oral solution: Shake well, and keep refrigerated; admixture stable for 30 days. When administering chewable tablets, at least two tablets should be given to ensure adequate buffering capacity (e.g. if the child's dose is 50 mg, administer two 25 mg tablets and not one 50 mg tablet). Can also crush / dissolve buffered tablets in water, apple juice or chocolate milk

Nucleoside Analogue Reverse Transcriptase Inhibitors

Appendix 4

DRUG	DOSAGE	ADVERSE REACTIONS	DRUG INTERACTIONS	SPECIAL INSTRUCTIONS
<p>Emtricitabine (FTC) (EMTRIVA)</p> <p><u>Preparation:</u> Oral solution 10mg/ml Capsules: 200mg</p>	<p><u>Neonatal/Infant Dose:</u> Not approved use in below age 3 months</p> <p><u>Pediatric Dose:</u> 3 months - 17 years Oral solution: 6mg/kg(maximum dose 240mg) once daily</p> <p>Capsules (for patients weighing > 33kg : 200mg once daily</p> <p><u>Adolescent/Adult:</u> 200mg once daily</p>	<p>More common: Headache, diarrhea, nausea, rash and skin discoloration (hyperpigmentation on palms and/or soles, predominantly observed in non-Caucasian patients)</p> <p>Less common (more severe): Neutropenia, lactic acidosis and severe hepatomegaly with steatosis</p>	<p>Do not use in combination with 3TC because of the similar resistance profiles and no potential additive benefit</p>	<p>Can be given without regard to food. It is recommended be administered on an empty stomach</p> <p>Oral solution should be refrigerated, can be kept at room temperature if used within 3 month</p>
<p>Lamivudine (3TC) EPIVIR</p> <p><u>Preparation:</u> Solution: 10mg/ml Tablets: 150mg</p>	<p><u>Neonatal Dose</u> (\leq 30 days old) : 2 mg/kg q12H daily</p> <p><u>3 months - 16 years pediatric Dose:</u> 4 mg/kg q12H up to a maximum of 150mg q12H daily</p> <p><u>Adolescent 12 years and older/ Adult Dose:</u> < 50kg: 4mg/kg q12H (maximum dose,150 mg) q12H daily \geq 50kg: 150mg q12H or 300mg once daily</p>	<p>More common: Headache, fatigue, decreased appetite, nausea, vomiting, diarrhea, skin rash and upper abdominal pain,</p> <p>Less common (more severe): Pancreatitis, peripheral neuropathy, anemia, decreased neutrophil count, increased liver enzymes and lipodystrophy syndrome. Lactic acidosis and severe hepatomegaly with steatosis (fatal cases have been reported)</p>	<p>TMP/SMX increases lamivudine blood levels; unknown significance.</p> <p>When used with ZDV may prevent emergence of resistance.</p> <p>Do not use in combination with FTC (Emtricitabine) because of similar resistance profiles and no potential additive benefit.</p>	<p>Can be given with or without food.</p> <p>For oral solution: Store at room temperature.</p> <p>Can also crush tablets. Decreased dosage in patients with impaired renal function.</p> <p>Patients should be screened for HBV infection before starting therapy; exacerbation of hepatitis has been reported after discontinuation of 3TC</p>
<p>Stavudine (d4T) ZERIT</p> <p><u>Preparations:</u> Solution: 1mg/ml Capsules: 30mg</p>	<p><u>Neonatal Dose Birth to 13 days of age:</u> 0.5mg/kg/dose every 12 hours</p> <p><u>Pediatric Dose:</u> 1 mg/kg q12H (max 30mg/dose)</p> <p><u>Adolescent/ Adult Dose:</u> 30 mg q12H</p>	<p>More common: Headache, gastrointestinal disturbances, diarrhea, nausea, vomiting, skin rashes, Lipoatrophy</p> <p>Less common (more severe): peripheral neuropathy, lipodystrophy, pancreatitis, Lactic acidosis, hepatomegaly with steatosis, muscle weakness (rare)</p>	<p>Should not be administered in combination with zidovudine (poor antiretroviral effect).</p> <p>Additive pancreatotoxicity in combination with pentamidine. Due to prolonged half-life of pentamidine, do not restart stavudine until one week after pentamidine therapy is concluded. Monitor amylase, lipase monthly. Avoid combination if possible.</p>	<p>Can be given with or without food.</p> <p>Reduce dose in renal impairment.</p> <p>For oral solution: Shake well and keep refrigerated; Solution stable for 30 days.</p>

Nucleoside Analogue Reverse Transcriptase Inhibitors

Appendix 4

DRUG	DOSAGE	ADVERSE REACTIONS	DRUG INTERACTIONS	SPECIAL INSTRUCTIONS
<p>Tenofovir Disoproxil fumarate(TDF) VIREAD</p> <p><u>Preparations:</u> Tablets: 300mg</p>	<p><u>Pediatric:</u> 2 - 8 years: 8mg/kg as suspension</p> <p>Over 8 years: 175mg/m² daily (under study)</p> <p>< 18 years: 6mg/kg daily (under study)</p> <p><u>Adolescent/ Adult Dose:</u> 300mg daily</p>	<p>Common: Diarrhea, Flatulence, Nausea, Vomiting Osteopenia Asthenia</p> <p>Less common: Lipodystrophy</p> <p>Serious: Lactic acidosis, Some fatal cases Hepatomegaly (Severe), Some fatal cases, Relapsing type B viral hepatitis, Steatosis of liver, Some fatal cases Acute renal failure, Fanconi syndrome, Renal impairment</p>	<p>Increased ddl plasma concentrations and risk of ddl toxicity (neuropathy, diarrhea, pancreatitis, severe lactic acidosis)</p>	<p>Food will enhance the absorption.</p> <p>May be taken without food or with a light meal if given together with didanosine enteric coated capsules, where as didanosine buffered tablets should be taken without food</p> <p>Monitor patients for ddl toxicity because serum concentration increased when given together</p> <p>Tablet may be crushed and dissolves in 100ml water in 20 minutes; grape juice may also be used</p>
<p>Zidovudine (ZDV) RETROVIR</p> <p><u>Preparations:</u> Syrup: 10mg/ml Capsules: 100mg</p> <p>Concentrate for i.v. infusion/ injection: 10mg/ml in 20ml vial</p>	<p><u>Usual Dose:</u> Oral: 160 mg/m² q8H, twice daily dosing has been used to improve compliance (180mg - 240mg per m²) q12H</p> <p><u>Infants and children over 90 days of age:</u> I.V. (intermittent infusion) 120 mg/m² q6H I.V. (continuous infusion) 20 mg/m²/h</p> <p><u>Full term and Infants:</u> < 90 days of age: 1.5mg/kg q6H</p> <p><u>Dose in Premature Infants</u> < 35 weeks gestational age: 1.5 mg/kg intravenously q12H or 2mg/kg orally q12H</p> <p>≥ 30 weeks gestation at birth: 1.5mg/kg or 2mg/kg orally q8H at 2 weeks of age</p> <p>< 30 weeks gestation at birth: 1.5mg/kg or 2mg/kg orally q8H at 4 weeks of age</p> <p><u>Neonatal Dose (Full-term and infants less than 90 days old</u> Oral: 2 mg/kg q6H I.V.: 1.5 mg/kg q6H</p> <p><u>Adolescent/ Adult Dose:</u> 200 mg tid or 300 mg bid</p>	<p>More common: Hematologic toxicity, including granulocytopenia and anemia (which may require transfusions), headache</p> <p>Less common (more severe): myopathy, myositis and liver toxicity.</p> <p>Rare: Lactic acidosis, severe hepatomegaly with steatosis (fatal cases)</p>	<p>Increased toxicity may be observed with concomitant administration of ganciclovir, TMP-SMX, acyclovir, interferon-alpha, fluconazole, methadone, pentamidine, phenytoin, probenecid, valproic acid</p> <p>Decreased renal clearance with cimetidine</p> <p>ZDV metabolism may be increased with co administration of rifampicin Clarithromycin decreases concentration of ZDV (administer 2 hrs apart)</p> <p>Avoid combination with stavudine (antagonism).</p>	<p>Best on an empty stomach. Can take with a non-fatty meal to minimize nausea. Fatty food result in a 57% decrease in ZDV concentrations</p> <p>May open capsules and give in small portion of food or 5-10ml cool water.</p> <p>Decrease dosage in severe renal impairment and significant hepatic dysfunction.</p> <p>Significant neutropenia or anemia may necessitate interruption of therapy until marrow recovery is observed; use of erythropoietin, filgrastim, or reduced ZDV dosage may be necessary.</p> <p>Infuse i.v. loading doses or intermittent dose over 1 hr. For i.v. solution: Dilute with D5W to conc. ? 4mg/ml; refrigerated diluted solution is stable for 24 hours.</p>

Non-Nucleoside Analogue Reverse Transcriptase Inhibitors

DRUG	DOSAGE	ADVERSE REACTIONS	DRUG INTERACTIONS	SPECIAL INSTRUCTIONS
<p>Nevirapine (NVP) VIRAMUNE</p> <p><u>Preparations:</u> Suspension: 10mg/ml</p> <p>Tablets: 200 mg</p>	<p><u>Dose</u> 200mg q12H (lead-in dosing of 200mg daily for first 14 days)</p> <p>Infants and children 2 months up to 8 years 4 mg/kg) once daily for 14 days followed by 7 mg/kg q12H</p> <p><u>Children 8 years and older</u> 4 mg/kg once daily for 14 days followed by 4 mg/kg q12H daily. The maximum daily dose is 400 mg</p> <p><u>Adolescent/ Adult Dose:</u> 200 mg q12H initiate therapy at half dose for the first 14 days. Increase to full dose if no rash or other untoward effects.</p>	<p>More common: Skin rash, Steven-Johnson syndrome, toxic epidermal necrolysis (some severe), fever, headache, nausea and abnormal liver function tests.</p> <p>Less common (more severe): Severe, life-threatening and rare cases fatal hepatotoxicity, including fulminant and cholestatic hepatitis, hepatic necrosis and hepatic failure (less common in children)</p>	<p>Induces hepatic cytochrome PH50 3A (CYP3A); auto-in duction of metabolism occurs in 2-4 weeks with a 1.5-2 times increase in clearance. Potential for multiple drug interactions.</p> <p>Before administration, the patient's medication profile should be carefully reviewed for potential drug interactions.</p> <p>Administration with protease inhibitors decreases IDV concentrations significantly; may also decrease ritonavir concentration. Not known if increased doses of protease inhibitors are needed.</p> <p>Fluconazole, voriconazole, clarithromycin, may increased NVP toxicity</p>	<p>Can be given without regard to food.</p> <p>Can crush tablets in water.</p> <p>May be administered concurrently with ddI.</p> <p>Patients experiencing rash during the 2-week lead in period should not have their NVP dose increased until the rash has resolved.</p> <p>If NVP dosing is interrupted for more than 7 days, NVP dosing should be restarted with once daily dosing for 14 days, followed by escalation to the full twice daily regimen.</p> <p>For suspension: Must be shaken well; store at room temperature.</p>
<p>Efavirenz (EFV) STOCRIN</p> <p><u>Preparations:</u> Oral solution 30mg/ml</p> <p>Tablets: 50mg, 200mg and 600mg</p>	<p><u>Usual Dose:</u> In PI &/or NRTI combination, 600mg od</p> <p><u>Children (17 yrs & under):</u> 13-15 kg 200mg 15-20 kg 250mg 20-25 kg 300mg 25-32.5 kg 350mg 32.5-40 kg 400mg Children above 40kg to use adult dose</p>	<p>More comon: skin rash, increased transaminase levels, nausea, dizziness, diarrhea, headache, psychiatric symptoms (hallucinations, confusion), agitation, vivid dreams.</p>	<p>Inducer of CYP3A4</p> <p>As IDV levels are decreased with coadministered, the dose of IDV needs to be increased to 1000mg q8hrs when taken with EFV.</p> <p>Monitoring of liver enzymes recommended when given together with ritonavir.</p> <p>Use with saquinavir as the sole PI is NOT recommended.</p> <p>Administration with clarithromycin may increased risk of rash use alternative like azithromycin</p> <p>Concentration of EFV will be decreased with co-administration of rifampicin</p> <p>The concomitant use of voriconazole and EFV is contraindicated due to significant decreases in voriconazole plasma concentrations. Concomitant use is also associated with significant increases in EFV plasma concentrations.</p>	<p>To improve tolerability of central nervous system side effects, bedtimedosing recommended during the first 2-4 weeks.</p> <p>May be taken with or without food.</p> <p>Pregnancy should be avoided in woman receiving EFAVIRENZ; barrier contraception, in combination with other contraception methods should be considered.</p>

Protease Inhibitors

DRUG	DOSAGE	ADVERSE REACTIONS	DRUG INTERACTIONS	SPECIAL INSTRUCTIONS
<p>Atazanavir (ATV) (REYATAZ)</p> <p>Preparation: Capsules: 100,150 and 200mg</p>	<p><u>Neonatal:</u> Drug should be avoided in patients under 3 months of age due to a risk of kernicterus</p> <p><u>Pediatric:</u> Age 4 - 13 years, 400mg once daily</p> <p><u>>13 years:</u> 600mg once daily</p> <p><u>Adult:</u> 400mg once daily</p>	<p>More common: Asymptomatic elevations in indirect bilirubin (30% of patients), jaundice (10% of patients), headache, fever, dizziness, nausea, vomiting, diarrhea and paresthesias.</p> <p>Less common (more severe): Prolongation of PR interval on ECG, abnormalities in AV conduction, rash, generally mild to moderate, Steven-Johnson Syndrome (rare)</p> <p>Rare: New onset of diabetes mellitus, hyperglycemia, ketoacidosis, exacerbation of existing diabetes mellitus, and elevation in serum transaminases</p>	<p>Increase QTc prolongation with clarithromycin administration, consider reduce dose by 50% or use alternative such as azithromycin</p> <p>Contraindicated Drugs: Terfenadine, Astemizole, Cisapride, Ergot Alkaloids, Midazolam, Rifampicin.</p> <p>Antacids decrease ATV concentrations, therefore ATV should be administered 2 hours before or 1 hour after these medications</p> <p>H-2 Receptor Antagonists, decrease ATV concentrations, recommended to separate dosing as far apart as possible, preferably by 12 hours.</p> <p>Proton-pump Inhibitors: Decrease ATV concentrations and therapeutic effect, hence coadministration is not recommended.</p>	<p>Should be taken with food to enhance absorption</p> <p>Atazanavir should be taken at least 1 hr before or after antacid or ddl</p> <p>Use with caution in patients with pre-existing cardiac conduction system disease or with other drugs known to prolong the PR interval (e.g calcium channel blockers, beta blockers, digoxin, verapamil)</p>
<p>Indinavir (IDV) CRIXIVAN</p> <p>Preparations: Capsules: 100, 200 mg & 400 mg</p>	<p><u>Dose</u> Investigational: 500 mg/m² q8H in children aged 4 to 15 years</p> <p><u>Neonatal Dose</u> Should not be administered to neonates due to the risks associated with hyperbilirubinemia (kernicterus)</p> <p><u>Adolescent/ Adult Dose</u> 800 mg q8H</p>	<p><u>More common:</u> Nausea, abdominal pain, headache, dizziness, metallic taste, asymptomatic hyperbilirubinemia (10%) and lipid abnormalities</p> <p><u>Less common</u> (more severe): Nephrolithiasis.</p> <p><u>Rare:</u> Hemolytic anemia and hepatitis (life threatening) New onset of diabetes, hyperglycemia, ketoacidosis, exacerbation of pre-existing diabetes mellitus</p>	<p>Not recommended for concurrent use: IDV increases the drug's metabolism, resulting in increased drug levels and potential toxicity: astemizole, terfenadine, cisapride, midazolam.</p> <p>IDV levels significantly reduced with concurrent use: Rifampicin.</p> <p>NVP coadministration may decrease indinavir serum concentration.</p> <p>Administration with other protease inhibitors: ritonavir decreases the metabolism of IDV and results in greatly increased IDV concentrations. Increased IDV serum concentrations and</p>	<p>Administer on an empty stomach 1 hour before or 2 hours after a meal (or can be administered with a light meal). When given in combination with RTV, meal restrictions are no longer necessary</p> <p>Adequate hydration required to minimize risk of nephrolithiasis (at least 48 oz = 1.44L of fluid daily in adult patients)</p> <p>If coadministered with ddl, give at least 1hour apart on an empty stomach.</p> <p>Decrease dose in patients with cirrhosis.</p> <p>Capsules are sensitive to moisture & should be stored in original container with dessicant.</p>

Protease Inhibitors

DRUG	DOSAGE	ADVERSE REACTIONS	DRUG INTERACTIONS	SPECIAL INSTRUCTIONS
			potential indinavir toxicity (nausea, headache, nephrolithiasis, asymptomatic hyperbilirubinemia) when coadministered with itraconazole and ketoconazole	
<p>Nelfinavir (NFV) VIRACEPT</p> <p><u>Preparations:</u> Powder for oral suspension: 50 mg per one level gram full scoop (200 mg per one level teaspoon)</p> <p>Tablets: 250 mg and film-coated 250mg</p>	<p><u>Dose</u> 20-30 mg/kg tid</p> <p><u>Children:</u> 3 months to 2 years of age a dose of 20 to 30 mg/kg/dose 3 times a day</p> <p>2 to 13 years of age is 45 to 55 mg/kg twice a day or 25 to 35 mg/kg three times a day with a meal. The maximum daily dose is 2500 mg</p> <p>Neonatal Dose Under study in PACTG 353: 10 mg/kg tid (investigational)</p> <p>Adolescent/ Adult Dose 750 mg tid</p>	<p>More common: Diarrhea (most common) asthenia, abdominal pain, rash and lipid abnormalities</p> <p>Less common (more severe): Exacerbation of chronic liver disease, lipodystrophy syndrome</p> <p>Rare: New onset of diabetes mellitus, hyperglycemia, ketoacidosis, exacerbation of existing diabetes mellitus, and elevation in serum transaminases</p>	<p>Before administration, the patient's medication profile should be carefully reviewed for potential drug interactions.</p> <p>Not recommended for concurrent use: Astemizole, terfenadine, cisapride, midazolam.</p> <p>NFV levels are greatly reduced with concurrent use of Rifampicin.</p> <p>Administration with other protease inhibitors: NFV increases levels of IDV; coadministration with ritonavir increases nelfinavir levels 1.5 fold, without change in ritonavir concentrations.</p>	<p>Administer with meal or light snack.</p> <p>For oral solution: Powder may be mixed with water, milk, pudding, ice cream, or formula (mixture is stable for up to 6 hours).</p> <p>Do not mix with any acidic food or juice because of resulting poor taste.</p> <p>Do not add water to bottles of oral powder; a special scoop is provided with oral powder for measuring purposes.</p> <p>Tablets readily dissolve in a small amount of water, mix a cloudy mixture well and consume it immediately. The glass should be rinsed with water and the rinse swallowed to ensure that the entire dose is consumed. Tablets can also be crushed & administered with pudding</p>
<p>Ritonavir NORVIR</p> <p><u>Preparations:</u> Oral solution: 80 mg/ml</p> <p>Capsules: 100 mg</p>	<p><u>Neonatal Dose</u> Investigational</p> <p><u>Dose:</u> 450 mg/m² q12H</p> <p><u>Pediatric dose:</u> Age > 1 month) 350-450 mg/m² q12H (not to exceed 600mg per dose)</p> <p>To minimize nausea/vomiting, initiate therapy at 250 mg/m² q12H and increase dose every 2 to 3 days by 50 mg/m²(2) twice daily until target dose or maximum tolerated dose is reached</p>	<p>More common: Nausea, vomiting, diarrhea, headache, abdominal pain, anorexia, circumoral paresthesias and lipid abnormalities.</p> <p>Less common (more severe): exacerbation of chronic liver disease, lipodystrophy syndrome.</p> <p>Rare: New onset diabetes mellitus, exacerbation of pre-existing diabetes, increased levels of triglycerides & cholesterol, hyperglycemia & diabetes, pancreatitis, hepatitis.</p>	<p>Ritonavir decreases levels of sulfamethoxazole.</p> <p>Increase metabolism of theophylline levels.</p> <p>Increase levels of warfarin & clarithromycin.,</p> <p>May increase or decrease digoxin levels.</p> <p>Administration with other protease inhibitors: Decrease the metabolism of indinavir & saquinavir & results in greatly increased concentrations of these drugs; increases nelfinavir concentration 1.5-fold.</p>	<p>Administration with food increases absorption and helps decrease gastrointestinal side effects.</p> <p>If administered with ddl, should be administered 2 hours apart.</p> <p>Oral capsules must be kept refrigerated but not required if capsules are used within 30days and stored below 25oC .</p> <p>For oral solution: Do not refrigerate. Shake well before use, recommended storage temperature is 20 - 25 oC.</p>

Protease Inhibitors

DRUG	DOSAGE	ADVERSE REACTIONS	DRUG INTERACTIONS	SPECIAL INSTRUCTIONS
Adolescent/ Adult Dose 600 mg q12H To minimize nausea/vomiting, initiate therapy at 300mg q12H and increase stepwise to full dose over 5 days as tolerated		Allergic reactions including bronchospasm, urticaria and angioedema		Oral solution has limited shelf-life (6 months), use by product expiration date. To minimize nausea, therapy should be initiated at a low dose & increase to full dose as tolerated. Techniques to increase tolerance: Mix oral solution with milk, chocolate milk or pudding, ice cream. Dulling the taste buds before administration by chewing ice. Coat the mouth by giving peanut butter to eat before the dose or administer strong- tasting foods such as cheese or strong- flavored chewing gum immediately after dose
Lopinavir/Ritonavir (LPV/r) (KALETRA) Preparations: Pediatric oral solution 80mg LPV/20mg RTV per ml Soft gelatin capsule: Each contain Lopinavir 133.3 mg Ritonavir 33.3mg	In children 6 months to 12 years of age, the recommended dose is as follows: 7 to < 15kg 12mg/kg LPV/ 3mg/kg RTV twice daily 15 - 40kg: 10mg/kg LPV/ 2.5mg/kg RTV twice daily < 40kg: 400mg LPV/ 100mg RTV twice daily <u>Adolescent/Adult:</u> 400mg/100mg (3 capsules or 5ml) twice daily	More common: Diarrhea, headache, asthenia, nausea and vomiting and rash, lipid abnormalities Less common (more common): lipodystrophy syndrome Rare: New onset of diabetes mellitus, hyperglycemia, ketoacidosis, exacerbation of pre-existing diabetes mellitus, hemolytic anemia, pancreatitis, elevation in serum transaminases and hepatitis	Contraindicated with amiodarone, piroxicam, astemizole/terfenadine, cisapride, alprazolam, midazolam, zolpidem	LPV/r tablets can be administered without regard to food LPV/r oral solution should be administered with food. A high fat meal increases absorption, especially of the liquid preparation. Should be refrigerated and if kept at room temperature up to 25°C , used within 2 months If coadministered with ddI, ddI should be given 1 hour before or 2 hours after LPV/r
Saquinavir INVIRASE (hard capsule) FORTOVASE (soft- gel capsule) Preparations: Capsule: 200 mg 400mg bid (Invirase)	<u>Neonatal Dose:</u> Unknown <u>Pediatric Dose:</u> SGC - Under Study in PACTG 397 : 50 mg/kg tid <u>Usual Dose:</u> Adolescent/ Adult Dose: 1200mg tid (Fortovase) 600mg tid (Invirase)	More common: Diarrhea, abdominal discomfort, nausea, headache, paresthesias skin rash and lipid abnormalities Less common (more severe): Exacerbation of chronic liver disease, lipodystrophy syndrome Rare: New onset diabetes mellitus, hyperglycemia, ketoacidosis, exacerbation of pre-existing diabetes mellitus, pancreatitis and elevation in serum transaminases	Drugs that induce CYP 3A4 may reduce saquinavir levels. Rifampicin reduces saquinavir levels greatly and should not be used in combination. Contraindicated Drugs: Terfenadine, Astemizole, Cisapride, Ergot Alkaloids, Midazolam, Rifampicin. Drugs that increase saquinavir levels: Ritonavir, Ketoconazole, Nelfinavir, Delavirdine.	Administer within 2 hours of a full meal to increase absorption (high fat meal preferred) Sun exposure can cause photosensitivity reactions; therefore, sunscreen or protective clothing is recommended Capsules should be kept refrigerated. Once brought to room temperature, use within 3 months.

TANNER STAGING IN ADOLESCENTS

Stage	Female					Male				
	Age range (years)	Breast growth	Public hair growth	Other changes	Age range (years)	Testes growth	Penis growth	Public hair growth	Other changes	
I	0-15	Pre-adolescent	None	Pre-adolescent	0-15	Pre-adolescent testes (2.5cm)	Pre-adolescent	None	Pre-adolescent	
II	8-15	Breast budding (thelarche); areolar hyperplasia with small amount of breast tissue	Long downy pubic hair near the labia, often appearing with breast budding at several weeks or months later	Peak growth velocity often occurs soon after stage II	10-15	Enlargement of testes; pigmentation of scrotal sac	Minimal or no enlargement	Long downy pubic hair, often appearing several months after testicular growth; variable pattern noted with pubarche	Not applicable	
III	10-16	Further enlargement of breast tissue and areola, with no separation of their contours	Increase in amount and pigmentation of hair	Menarche occurs in 2% of girls late in stage III	10.5-16.5	IFurther enlargement	Significant enlargement, especially in diameter	Increase in amount curling	Not applicable	
IV	10-17	Separation of contours; areola and nipple form secondary mound above breast tissue	Adult in type but not in distribution	Menarche occurs in most girls in stage IV, 1-3 years after thelarche	Variable 12-17	Further enlargement	Further enlargement especially in diameter	Adult in type but not in distribution		
V	12.5-18	Large breast with single contour	Adult in distribution	Menarche occurs in 10% of girls in stage V	13-18	Adult in size	Adult in size	Adult in distribution (medial aspects of thighs; lineae alba)	Body hair continues to grow and muscles continue to increase in size for several months to years; 20% of boys reach peak growth velocity during this period	

Investigations for Opportunistic infections*

Opportunistic Infections	Specimen	Investigation	Notes
Bacterial Pneumonia	• Blood	• Culture	<i>Streptococcus pneumoniae</i> , <i>Haemophilus influenzae</i> type <i>b</i> (<i>Hib</i>), <i>Staphylococcus aureus</i> , or <i>Escherichia coli</i>
	• Induced Sputum • Pleural Fluid • Bronchoalveolar Lavage (BAL)	• Gram Stain, Culture	
Herpes zoster	• Endotracheal Aspirate	• Gram Stain • Culture And Sensitivity	Zar HJ, Tannenbaum E, Hanslo D, Hussey G. Sputum induction as a diagnostic tool for community acquired pneumonia in infants and young children from a high HIV prevalence area. <i>Pediatr Pulmonol</i> 2003;36:58.
	• Skin, Conjunctiva, Or Mucosal Lesion Scrapings	• Direct Immunofluorescence • Tzanck Smear • Culture • PCR	
Cutaneous fungal infections	• Skin Scrapings • Biopsy	• KOH Preparation • Culture	
	• Mucosal Scraping	• KOH Preparation • Culture	
Pneumo jiroveci pneumonia(carrinii)	• Induced Sputum • BAL • Endotracheal Aspirate • Lung Biopsy	• Silver Stains • Monoclonal Immunofluorescent Antibodies	Poor negative predictive value for sputum Bronchoscopy with BAL is the diagnostic procedure of choice for infants

Investigations for Opportunistic infections*

Opportunistic Infections	Specimen	Investigation	Notes
<i>Pneumo jiroveci</i> pneumonia(carinii)	<ul style="list-style-type: none"> Lung Biopsy 	<ul style="list-style-type: none"> Histopathology 	<p>Alvarez F, Bandi V, Slager C, Guntupalli KK. Detection of Pneumocystis carinii in tracheal aspirates of intubated patients using calcofluor-white (Fungi-Fluor) and immunofluorescence antibody (Genetic Systems) stains. Crit Care Med. 1997 Jun;25(6):948-52. Search Pubmed endotracheal Suction Pneumocystis = 2 titles one relevant</p> <p>Histopathology shows alveoli filled with eosinophilic, acellular, proteinaceous material that contains cysts and trophozoites but few inflammatory cells</p>
	<ul style="list-style-type: none"> Biopsied Lung Peripheral Lymph Node Other Tissue Depending On Location Of Disease) 	<ul style="list-style-type: none"> Histopatology 	<p>Two PCR commercial kits are available for rapid, direct detection of M. tuberculosis, and both are labeled for use on sputum only. One is labeled for use on sputum only with AFB detected on the smear. When these tests are used for other specimens, sensitivity and specificity might be unsatisfactory.</p>
<i>Penicillium marneffe</i>	<ul style="list-style-type: none"> Sputum Induced Sputum Gastric Lavage BAL Blood 	<ul style="list-style-type: none"> Culture Conventional/Automat ZN Stain PCR Mycobacterial Culture 	<p>Specimens should be cultured with radiometric culture methods and DNA probes for species identification. M. tuberculosis can be isolated and identified in 7-14 days.</p>
	<ul style="list-style-type: none"> Skin lesions Blood Lymph nodes Bone marrow 	<ul style="list-style-type: none"> Direct microscopy Culture 	

* Only the more common opportunistic infections are discussed

Treatment for opportunistic Infections*

Pathogen	Preferred therapies and duration	Alternative therapies	Other options/issues
Pneumocystis jirovecii pneumonia	Trimethoprim-sulfamethoxazole (TMP/SMX) 15-20 mg/kg body weight TMP plus 75-100 mg/kg body weight SMX administered IV or Oral 3 or 4 times daily for 21 days	Intolerant or clinical treatment failure after 5-7 days of TMP/SMX therapy: Pentamidine 4 mg/kg body weight intravenously once daily	Indications for corticosteroids: - PaO ₂ <70 mm Hg at room air or alveolar-arterial oxygen gradient >35 mm Hg Continue secondary prophylaxis
Mycobacterium tuberculosis (TB)	Intensive Isoniazid (INH) 10-15 mg/kg(max: 300 mg/day) oral daily Rifampicin 10-20 mg/kg body weight pyrazinamide 20-40 mg/kg (max: 2 g/day) body weight oral daily ethambutol 15-25 mg/kg body weight (max: 1.0 g/day) oral daily Continuation phase (for drug sensitive TB): Daily: Isoniazid 10-15 mg/kg body weight (max: 300 mg/day) oral daily plus rifampicin 10-20 mg/kg body weight (max: 600 mg/ day) oral daily OR Intermittent: Isoniazid 20-30 mg/kg body weight (max: 900 mg/day) by mouth once daily administered two to three times a week plus rifampicin 10-20 mg/kg body weight (max: 600 mg/day) by mouth once daily administered two to three times a week	Alternative drug for ethambutol is streptomycin Ethionamide should be used for tuberculosis meningitis	Pyridoxine should be administered if isoniazid is administered In antiretroviral-naïve child, initiate therapy for TB 4-8 weeks before starting antiretroviral drugs Optimal timing of commencement of HAART in newly diagnosed HIV infected children with TB disease remains unclear. In general, antiretroviral therapy should be commenced at least 1-2 months after commencement of antituberculous therapy. For children already on HAART when TB is diagnosed, treatment should be continued however alteration of drug combinations may be required to minimize potential toxicities and drug-drug interactions. Treatment duration Pulmonary TB: 9 months for HIV infected child

Appendix 7

Pathogen	Preferred therapies and duration	Alternative therapies	Other options/issues
Oropharyngeal Candida	Fluconazole 3-6 mg/kg body weight (max: 400 mg/dose) by oral daily for 7-14 days	(fluconazole refractory): Itraconazole cycloheximide oral solution 2.5 mg/kg body weight by mouth twice daily (max: 200 - 400 mg/day) for 7-14 days OR Amphotericin B oral suspension 1ml (100 mg/ml) by mouth four times daily for <14 days For patients not responding to acyclovir:	Plenaar, Young & Holmes Cochrane Database 2006 Due to only one study in children it is not possible to make recommendations for treatment or prevention of oropharyngeal candidiasis
<i>Varicella zoster virus</i>	Chickenpox/ Zoster: Severe Acyclovir 10 mg/kg IV three times daily for 7 days or until no new lesions have appeared for 48 hours Children with mild immunosuppression and mild disease Acyclovir 20 mg/kg oral (max: 800 mg/dose) four times daily for 7 days or until no new lesions have appeared for 48 hours	Foscarnet 40-60 mg/kg IV three times daily for 7-10 days <i>Currently not available for use in Malaysia</i>	
<i>Penicillium marneffei</i>	Amphotericin B 0.6 - 1.0mg/kg per day for two weeks followed by maintenance treatment with itraconazole	http://www.aidsmap.com/cms/1032622.asp	Suppressive treatment will be necessary for as long as the immune system remains severely impaired

* Only the more common opportunistic infections are discussed

Table 2 LIST OF HIV DRUGS AVAILABLE IN MALAYSIA

Abacavir 300mg Tab
Abacavir oral solution 20mg/ml, 240ml
Didanosine 100mg Tab
Didanosine EC 250mg Cap
Didanosine EC 400mg Cap
Didanosine pediatric powder for oral suspension 2G
Efavirenz 200mg Cap
Efavirenz 50mg Cap
Efavirenz 600mg Tab
Indinavir 400mg Cap
Lamivudine 150mg Film-coated Tab
Lamivudine oral solution 10mg/ml, 240ml
Lopinavir 133.3 mg + Ritonavir 33.3 mg Cap
Lopinavir 80mg + Ritonavir 20mg/ml Solution, 160ml
Nevirapine tablet 200mg
Ritonavir 100mg Cap
Ritonavir 80mg/ml solution, 240ml
Saquinavir 200mg Cap
Stavudine 30mg + Lamivudine 150mg + Nevirapine 200mg Tab
Stavudine 30mg Cap
Stavudine 40mg + Lamivudine 150mg + Nevirapine 200mg Tab
Stavudine 40mg Cap
Zidovudine 100mg Cap
Zidovudine 300mg Cap + Lamivudine 150mg Tab
Zidovudine 10mg/ml Syrup, 200ml
Zidovudine 10mg/ml, 20ml IV Inj

Appendix 9

Additional Resources**Infant feeding**

http://www.who.int/nutrition/publications/HIV_IF_guide_for_healthcare.pdf

http://www.who.int/nutrition/publications/HIV_IF_Transmission.pdf

HIV and Infant Feeding Update

http://whqlibdoc.who.int/publications/2007/9789241595964_eng.pdf

http://www.uniteforchildren.org/knowmore/files/Module_4PM.pdf

HIV and Infant Feeding. <http://www.avert.org/hiv-breastfeeding.htm>

Adherence

HIV/AIDS Primary Care Guide. Adherence in the Pediatric HIV Population Ana M. Puga, MD

http://www.faetc.org/PDF/Primary_Care_Guide/Chapter_32-Adherence_in_the_Pediatric.pdf

Baylor International Pediatric AIDS Initiative Educational Resources. Primer on Pill Swallowing.

2007 <http://bayloraids.org/resources/pillprimer/>

Opportunistic Infections

HIV/AIDS Primary Care Guide. Prevention and Management of Opportunistic Infections in Children Daniela Chiriboga, MD Patricia Emmanuel, MD.

http://www.faetc.org/PDF/Primary_Care_Guide/Chapter_31-Management_of_OIs_in_Children.pdf

Disclosure, Counselling & Supportive Care

Guidelines for Counselling Children Who are Infected with HIV or Affected by HIV and AIDS. South African AIDS Trust. 2003

<http://www.satregional.org/attachments/Publications/Skills%20Training%20E/CABA.pdf>

Therapeutic education: Recommendations regarding disclosure of HIV status to children under ARV In MSFproject. MSF Paris. 2005

http://www.who.int/hiv/topics/vct/toolkit/additional_resources/MSF_recommendations_disclosure.pdf

School HIV/AIDS Policy Tool Kit Wisconsin Department of Public Instruction 2003. <http://dpi.state.wi.us/sspw/pdf/hivtoolkit.pdf>

HIV/AIDS Primary Care Guide. Supportive Care for HIV-Infected Children and Their Families Gwendolyn B. Scott, MD

http://www.faetc.org/PDF/Primary_Care_Guide/Chapter_34-Supportive_Care.pdf

HIV/AIDS Primary Care Guide. Adolescent Issues Lawrence B. Friedman, MD, Jeri A. Dyson, MD, Mobeen H. Rathore, MD

http://www.faetc.org/PDF/Primary_Care_Guide/Chapter_35-Adolescent_Issues.pdf

HIV in Schools. Good practice guide to supporting children infected or affected by HIV. Magda Conway 2005

http://www.ncb.org.uk/dotpdf/open%20access%20-%20phase%201%20only/hivforum_schoolsgpg.pdf

Palliative Care

HIV/AIDS Palliative Care Guidance#1 - For the United States Government in-Country Staff And Implementing Partners. The President's Emergency Plan for AIDS Relief. Office of the U.S. Global AIDS Coordinator 2006. <http://www.state.gov/documents/organization/64416.pdf>

Schools

Guidance On First Aid For Schools. Department for Employment and Education, UK. <http://www.teachernet.gov.uk/doc/4421/GFAS.pdf>

LIST OF ABBREVIATIONS

ATV	Atazanavir
3TC	Lamivudine
ZDV	Zidovudine
D4T	Stavudine
DDI	Didanosine
EFV	Efavirenz
FTC	Emtricitabine
IDV	Indinavir
IPV	Injected Polio Vaccine
INH	Isoniazid
LPV/r	Ritonavir-boosted lopinavir (Kaletra)
NLV	Nelfinavir
NNRTI	Non-nucleoside reverse transcriptase inhibitors
NRTI	Nucleoside reverse transcriptase inhibitors
NVP	Nevirapine
PI	Protease inhibitors
RTV	Ritonavir
SQV	Saquinavir
sdNVP	Single -dose Nevirapine
TDF	Tenofovir
TMP-SMX	Trimethoprim- Sulfamethoxazole
ZDV	Zidovudine
ZDV+3TC	Zidovudine+ Lamivudine

AIDS	Acquired immunodeficiency syndrome
ARV	Antiretroviral
ART	Antiretroviral therapy
BCG	Bacillus Calmette-Guérin
CMV	Cytomegalovirus
EC	Enteric coated
FBC	Full blood count
GMT	Geometric Median Titre
HAART	Highly Active Anti-Retroviral Therapy
Hib	Haemophilus influenzae B
HPV	Human papilloma virus
HIV	Human Immunodeficiency Virus
IP	Intrapartum
IRIS	Immune reconstitution inflammatory syndrome
LIP	Lymphocytic interstitial pneumonitis
MMR	Mumps, measles and rubella
MTCT	Mother-to-child transmission
OPV	Oral polio vaccine
PCV	Pneumococcal conjugate vaccine
PMTCT	Prevention of mother-to-child transmission
pVL	Plasma viral load
PCP	Pneumocystis jiroveci Pneumonia
OI	Opportunistic infection
RCT	Randomised controlled trial
sd	Single dose
STIs	Sexually transmitted infections
TB	Tuberculosis
VLBW	Very low birth weight
WHO	World Health Organisation

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LEVELS OF EVIDENCE SCALE

Level	Strength of evidence	Study design
1	Good	Meta-analysis of RCT, Systematic review
2	Good	Large sample RCT
3	Good to Fair	Small sample RCT
4		Non-randomised controlled prospective trial
5	Fair	Non-randomised controlled prospective trial with historical control
6	Fair	Cohort studies
7	Poor	Case-control studies
8	Poor	Non-controlled clinical series, descriptive studies multi-centre
9	Poor	Expert committees, consensus, case reports, anecdotes

SOURCE: ADAPTED FROM CATALONIAN AGENCY FOR HEALTH TECHNOLOGY ASSESSMENT, (CAHTAR) SPAIN

GRADES OF RECOMMENDATION

A	At least one meta analysis, systematic review, or RCT, or evidence rated as good and directly applicable to the target population
B	Evidence from well conducted clinical trials, directly applicable to the target population, and demonstrating overall consistency of results; or evidence extrapolated from meta analysis, systematic review, or RCT
C	Evidence from expert committee reports, or opinions and /or clinical experiences of respected authorities; indicates absence of directly applicable clinical studies of good quality

SOURCE: MODIFIED FROM SCOTTISH INTERCOLLEGIATE GUIDELINES NETWORK (SIGN)