

Recommendations on the Management of HIV Infection in Infants and Children

*Scientific Committee on AIDS
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INTRODUCTION

1. In Hong Kong, the number of known infections in children has remained small. A majority of the infected children in the mid- and late-eighties were haemophiliacs or recipients of contaminated blood. Mother-to-child transmission is now the single most important mode of HIV infection in children in Hong Kong. Worldwide, it accounts for over 90% of all paediatric HIV infections.
2. Early identification of human immunodeficiency virus (HIV)-infected pregnant women prior to delivery could effectively reduce perinatal transmission of the infection. However, treatment of HIV-infected women will not completely eliminate all mother-to-child infections. The proportion of infections occurring *in utero* is estimated to be approximately 25% to 40% among children who are not breast-fed. (1) Mathematical modeling suggests that much of this *in utero* transmission occurs relatively late in gestation. (2) The absolute risk for *in utero* transmission is estimated to be 5% or 6%, and for intrapartum transmission, approximately 13% to 18%. Therefore, a small number of infants may still be infected before the diagnosis of the mother. Another reason of perinatal infection is that not all HIV-infected pregnant women may be diagnosed and can receive therapy in time.
3. Advances in HIV treatment are changing the landscape of HIV/AIDS in the clinical setting. Prior to effective viral suppressive therapy, a majority of the infected infants developed marked immunosuppression and AIDS-defining conditions by approximately seven years of age. *Pneumocystis carinii* pneumonia (PCP), HIV encephalopathy, developmental delay, failure to thrive and recurrent bacterial infections were commonly observed problems. Today, children receiving antiretroviral agents often have different clinical and pharmacokinetic profiles, and have slightly different side effects as compared to adults.
4. The current set of guidelines is developed by the Scientific Committee on AIDS (SCA) to suggest a standard approach in the management of infants and children perinatally exposed and/or infected with HIV, based on scientific evidence and international experience and recommendations. (3,4,5). However, since research in children usually lags behind that in adults, some recommendations are extrapolated from adult data. A local perspective is emphasised in the preparation of the document. This document supersedes *Guidelines on Management of HIV infection Children* published in 1995.

PRINCIPLES

5. The guiding principles in the following recommendations are:
- (a) HIV-exposed or infected children should be evaluated as soon as possible after birth for the diagnosis of HIV infection.
 - (b) Postnatal antiretroviral treatment should be completed according to the perinatal prophylaxis regimen chosen for the mother.
 - (c) Prophylaxis against PCP should normally be commenced at 6 weeks of age for all infants born to an HIV-infected mother.
 - (d) Early treatment of HIV-infected infants regardless of clinical and immunologic parameters is the preferred approach for achieving viral suppression.
 - (e) Childhood immunization is an important part of the clinical management for HIV infected children, the practice of which is similar to that for healthy infants and children with slight adjustment.
 - (f) Highly Active Antiretroviral Therapy (HAART) is the standard in management of HIV-infected children, if antiretroviral therapy is indicated.
 - (g) A multispecialty, multidisciplinary approach involving the following expertise is needed for the comprehensive care of HIV-infected children: paediatric infectious disease, paediatric neurology, paediatric cardiology, nursing, social work, psychology, nutrition, and pharmacology. Life-long continuous care is recommended.
 - (h) Recommendations for therapy and management will have to be updated frequently as the management of HIV infection in infants, children and adolescents is rapidly evolving and becoming increasingly complex.
 - (i) A mechanism shall be in place to enhance the local knowledge-base in HIV management in children, and the exposure (infection or otherwise) of children to antiretroviral treatment.

DIAGNOSIS OF HIV INFECTION IN CHILDREN

6. Diagnosis of HIV infection in perinatally exposed children can be made by the culture of peripheral blood mononuclear cells (PBMC) or HIV DNA polymerase chain reaction (PCR). International literature has recommended DNA PCR as the virologic method for early diagnosis of HIV infection in

infants. The test, if available, should be performed within the first 48 hours of life. This method has very good sensitivity and specificity for detecting the presence of the virus within PBMCs. The sensitivity of the HIV DNA PCR has been studied: 38% of infected infants were positive within 48 hours of life, 93% were positive by 14 days of age, and 96% were positive by 4 weeks of age. Infants with 2 positive results can be determined to be infected.(6) Infants with negative tests during the first 6 weeks of life should be re-tested between 1 to 2 months of age, and again between 4 to 6 months of life. (4) Initially there was concern that prophylactic antiretroviral treatment of the infant might interfere with the early diagnosis of HIV infection. However, to date, zidovudine (ZDV) has not been shown to decrease the sensitivity and predictive values of virologic assays. (4,7)

7. Currently, both HIV culture and HIV DNA PCR are not available as routine diagnostic tests. In clinical practice, HIV RNA PCR assay is recommended as the alternative for diagnostic purpose in Hong Kong. The latter assay is available in clinical laboratories and can be used to test for plasma virus. There has been concern about potential false-positive results near the assay's limit of detection. (8,9,10) In all circumstances, clinical correlation and the advice of virologist should be sought in the interpretation of the results.

8. A child born to an HIV-infected mother is considered uninfected if
- (a) there is no clinical evidence of HIV infection, and
 - (b) in the absence of breastfeeding, 2 or more virologic determinations (culture or PCR) are persistently negative, both of which are performed at 1 month of age or older, and one of which is performed at 4 months of age or older, or
 - (c) 2 negative HIV antibody tests at least 1 month apart, performed at greater than 6 months of age.(6)

CARE OF INFANT BORN TO AN HIV-INFECTED MOTHER

Antiretroviral therapy

9. All infants born to HIV-infected women who have been started on the ACTG 076 prophylaxis regimen should receive a 6-week course of oral ZDV. ZDV is also recommended for the infant born to an HIV-infected woman who has received no antiretroviral therapy during pregnancy or delivery.(11) Alternatives include the use of nevirapine or ZDV/ lamivudine (3TC) combination or ZDV/nevirapine combination. If the mother is not diagnosed until labour and has received an alternative antiretroviral prophylaxis regimen, the infant should receive the same antiretroviral agent according to the regimen. Breastfeeding by their HIV-infected mothers is contraindicated in

Hong Kong since there are safe alternatives to breast milk. (refer to the Scientific Committee on AIDS *Recommended Clinical Guidelines on the Prevention of Perinatal HIV Transmission* published in April 2001, reference 13)

Laboratory monitoring

10. Complete blood picture (CBP) and differential count should be performed on the newborn as a baseline evaluation before administration of ZDV. Anaemia is the primary short-term complication of the 6-week ZDV regimen in the neonate. Repeat measurement of haemoglobin is required during and after the completion of the regimen. Infants who have anaemia at birth or who are premature warrant more intensive monitoring.

11. CD4+ lymphocyte count and percentage should be monitored at 1 and 3 months of age and then continued at 3-month-interval until HIV infection in the infant can be ruled out.

12. Quantitative immunoglobulins should be measured when the infant is 4 to 6 months of age.

Prophylaxis for *Pneumocystis carinii* pneumonia (PCP)

13. PCP used to be the most common AIDS presenting illness in children before the days of effective antiretroviral therapy. It occurs most often between 3 and 6 months of age when many HIV-exposed infants have not yet been identified as being infected. In 1995, CDC revised the recommendation for PCP prophylaxis in HIV-exposed infants. (12) (Table 1) All infants born to HIV-infected women should begin prophylaxis at 6 weeks of age, following completion of the ZDV prophylaxis regimen, regardless of CD4+ lymphocyte counts or percentage. The drug regimens are shown in Table 2.

CARE OF THE HIV-INFECTED INFANT OR CHILDREN

14. The following recommendations apply to all newly diagnosed HIV infected children. Once HIV infection is established in a child, the following initial steps should be taken:

Complete and detailed medical history and physical examination

15. Depending on the individual situation, baseline assessment of the child and family may be done in the inpatient setting. This approach has several advantages: more time can be spent during the initial encounter between the family and the medical team; the family can familiarise themselves with the medical team and the hospital; doctors and nurses can observe the social

dynamics of the family; and the initiation of antiretroviral drugs can be supervised and monitored.

16. Attention should be paid to clinical symptoms commonly seen in HIV infection, e.g., failure to thrive, developmental delay, lymphadenopathy, hepatomegaly, splenomegaly, candidiasis. The clinical categorisation of paediatric HIV infection is detailed in Table 3. If the child is the first member of the family diagnosed with HIV infection, both parents and other siblings should also be counseled and evaluated for HIV infection.

Baseline and follow-up investigations

17. The main investigations are T cell subset enumeration and viral load measurement. Other investigations are also included in this section.

(a) T-cell subsets

Absolute CD4+ lymphocyte number and percentage are surrogate markers of disease progression in HIV infection and should be monitored. Profound decrease in CD4+ lymphocyte counts in the first year of life signifies rapid progression of HIV disease and indicates the immediate need for highly active antiretroviral therapy (HAART). The immunological classification system for HIV infection in children is in Table 4.

(b) HIV virus load

Quantification of free virus in plasma can be performed using HIV RNA assays. The dynamics of HIV RNA burden observed in infants is very different from that of adults. Perinatally infected infants exhibit primary HIV viraemia in the first month of life when they have a relatively immature system. They exhibit an extremely high plasma virus load, commonly greater than 10^6 copies/ml plasma by HIV RNA PCR. Over time the virus load tends to fall. In general, elevated HIV RNA viral load after the first month of life correlates with rapid disease progression, although some children with high HIV RNA levels in the first year do not progress as rapidly. (13, 14) Due to considerable inpatient biologic variability in HIV RNA levels, only changes greater than 0.7 log in HIV RNA viral load in children under 2 years and those greater than 0.5 log in children older than 2 years should be considered significant.

(c) Other laboratory investigations

Baseline assessment includes CBP with differentials, liver and renal function tests, amylase, lipid, lipase levels, lactate dehydrogenase and quantitative immunoglobulins. Baseline antibody titres should be considered for toxoplasma, cytomegalovirus (CMV), Epstein-Barr virus, varicella-zoster virus, herpes simplex virus (HSV) and hepatitis viruses. Initial titres drawn at the neonatal period would reflect the immune

status of the mother. Repeat testing should be done at 12 months of age and then annually if they are negative. The results provide information about these children's exposure and susceptibility to specific infection. For example, CMV negative HIV infected children should receive CMV negative blood in the case of transfusion and if unavailable, leukofiltered blood should be used if possible. For older children, functional antibodies against common antigens could be assessed. This is usually achieved by measuring their immune status after routine immunization, e.g. IgG against measles and tetanus. Since primary CMV infection in the first months of life has been associated with an increase in HIV replication, urine culture for CMV may also be obtained in the first 6 months of age.

(d) Other evaluations

- i) Chest X-ray – A baseline chest X-ray (CXR) should be obtained and then annually even in asymptomatic children. This test identifies mediastinal enlargement, lung lesions, lymphoid interstitial pneumonitis (LIP) and cardiomegaly. Patients with chronic lung changes should also have oxygen saturation measured at every visit.
- ii) Cardiac assessment – HIV cardiomyopathy starts early in life. When patients are examined by ECG or during autopsy, cardiac abnormalities are detected more often than expected from physical examination. A study on HIV-infected children using ECG has shown that subclinical cardiac abnormalities are common, which may be persistent and often progressive. (15) A baseline and annual cardiac assessment that includes at least a CXR and an ECG is recommended.
- iii) Visual screening - Children who can cooperate with the examiner should have an annual ophthalmology examination. Children with immune category 3 (table 4) should preferably be examined by an ophthalmologist every 6 months, especially if they are seropositive for toxoplasmosis or CMV.
- iv) Neurodevelopmental assessment - For older children, as well as young infants with neurologic deficits, imaging of the brain (MRI or CT) should be performed at baseline for evaluation of possible brain atrophy. Older children are referred for a baseline neurodevelopmental assessment by a neurologist. Infants can be referred after 6 months of age if there are no neurologic symptoms, and earlier if they are symptomatic.
- v) Psychosocial assessment - The diagnosis of HIV infection in a child is very devastating for a family. Since the care of an HIV-infected child is a chronic issue, clinicians should aim to establish a long-

term relationship with the patient and the family. The establishment of trust and rapport greatly improves adherence to medical treatment. The family should be assessed by the medical social worker to address the needs for social service or financial support. Members of the family should be offered referral to the clinical psychologist as appropriate.

Antiretroviral Therapy

18. The goals of antiretroviral therapy include:

(a) Life prolongation

(b) Prevention of disease progression

(c) Maintenance or improvement of quality of life.

19. Based on our current understanding of the viral dynamics and disease pathogenesis, the best way to achieve these goals is to suppress HIV replication to very low levels indefinitely. Since drug resistance and virologic failure may be inevitable if viral replication persists in the face of therapy, the immediate goal of therapy should be complete viral suppression. With the implementation of universal testing of pregnant women for HIV infection, most HIV infants can be diagnosed in the first month of life. With the commitment of child carers to adherence to long-term therapy, early treatment of these recently infected infants offers the best chance for complete viral suppression. Initiating therapy very early in primary infection may also prevent the spread of HIV to long-lived reservoirs like memory CD4+ T lymphocytes.

20. Since the selection for resistant virus by non-adherence may be worse than ongoing replication of untreated wild type virus, the caregivers need to have a good understanding of the importance of adherence before initiating therapy. It is usually a struggle to administer medications to young children and it is not uncommon that they spit out unpalatable medications. Caregivers should be advised to contact the clinicians immediately if the child repeatedly vomits the antiretroviral drugs. It must be emphasised that the effectiveness of an antiretroviral regimen is directly related to adherence.

21. The following are the recommended principles in the use of antiretroviral treatment in infants and children, and the rationale involved.

(a) Early treatment of all infants recently diagnosed of HIV infection is recommended.

Although only limited data are available on the effectiveness of early combination antiretroviral therapy in children, studies on primary infection in adults have demonstrated that early aggressive treatment might preserve immune function, decrease viral seeding, lower the viral set point. Recent data from a multicentre observational cohort

study suggest that infected children exposed to ZDV during pregnancy or birth had more rapid disease progression if effective multidrug therapy was not initiated.(16) These studies owe support to the early treatment of HIV infected infants

- (b) *All HIV infected children with clinical symptoms of HIV infection (clinical categories A, B or C) or evidence of immune suppression (immune categories 2 or 3) (Table 3 and 4) should be treated, regardless of age or virus load. (17)*

It is recommended that all HIV-infected children be treated as soon as possible, with the exception of children older than 1 year with normal immune status and a low virus load. (4)

- (c) *Antiretroviral therapy may be initiated in infected children aged < 1 year regardless of age or symptom status.*

The preferred approach is to initiate therapy in all HIV-infected children, regardless of age or symptom status. Such an approach would ensure treatment of infected children as early as possible in the course of disease with the highest chance of intervening before immunologic deterioration.

- (d) *Although early initiation of antiretroviral therapy is favoured, there may be situations when deferment of treatment can be considered.*

In asymptomatic children aged ≥ 1 year with normal immune status and a low viral load in whom the risk for clinical disease progression is considered low, and when other factors including the issues of drug safety and concern for adherence due to unreliable caregivers, postponing treatment may be justified. When treatment is deferred, antiretroviral therapy should be initiated when i) HIV RNA levels increase significantly (> 0.7 log in children under 2 years and >0.5 log in children over 2 years), ii) CD4+ decline into category 2, iii) development of HIV related symptoms, iv) HIV RNA $>10^5$ copies/ml in any child or v) in children older than 30 months who have HIV RNA levels $> 10^4$ copies/ml.

- (e) *The regimen should be effective in achieving a sustained viral suppression and the side effects should be tolerable.*

Antiretrovirals will need to be administered for many years, if not life-long. The choice of initial therapy needs to take several issues into consideration. Potential limitations in subsequent treatment options due to cross-resistance should it occur would also need to be taken into consideration.

- (f) *Highly Active Antiretroviral Therapy (HAART) is indicated*

When antiretroviral treatment is indicated, the highly active anti-retroviral therapy (HAART) should be prescribed. The recommended

regimen includes 2 nucleoside reverse transcriptase inhibitors (NRTIs) and 1 protease inhibitor (PI). The rationale for the choice is to attain maximal suppression of virus replication. This approach has been successful in children with reduction of HIV RNA to undetectable levels. (18,19,20) While waiting for more clinical trials of antiretroviral drugs on children, some information regarding the efficacy of these drugs can be extrapolated from trials involving adults. The absence of clinical trials addressing pediatric-specific manifestations of HIV infection does not preclude the use of any approved antiretroviral drug in children. All antiretroviral drugs approved for treatment of HIV infection may be used for children when indicated — irrespective of labeling notations. The characteristics of antiretroviral drugs are listed in Table 5, 6 and 7.

For clinicians and patients who prefer to spare the use of protease inhibitors, an option is to initiate therapy with 2 NRTIs with a non-analogue nucleotide reverse transcriptase inhibitor (NNRTI), e.g., nevirapine.

Prophylaxis for PCP

22. The recommendations are covered earlier (paragraph 13).

Prevention of other opportunistic infections

23. Caregivers play a role in preventing opportunistic infections in the infants. Caregivers should be advised to avoid consumption of raw or undercooked meat, seafood or poultry, unpasteurized milk products as well as food prepared under doubtful hygiene conditions to decrease the risk of enteric infection. They should also be advised of the potential risks of infection from pets, e.g. cats that can transmit toxoplasma and bartonella, and turtles and reptiles that can transmit salmonella. Exposure to young farm animals should also be avoided to reduce the risk of cryptosporidiosis. On the other hand, HIV infected children should not drink or swim in lake or river water to reduce the risk of *Cryptosporidium* or *Giardia* infection. Practice of good handwashing and personal hygiene should be emphasised.

Immunization

24. HIV-exposed and infected infants and children should receive standard paediatric immunisations with a few exceptions. Inactivated polio vaccine (IPV) should be given instead of the live oral polio vaccine (OPV). The OPV-1 now routinely given to all local newborn should be avoided in babies born to HIV infected mothers. Even if the child is ultimately found to be uninfected, IPV should be continued if the child lives with HIV-infected persons. When polio vaccination is required in household members of an HIV infected person, IPV is also indicated.

25 Live vaccines are normally not used in immunocompromised hosts. Measles-mumps-rubella (MMR) vaccination is only recommended for HIV-exposed and HIV-infected children who are not severely immunocompromised (CDC immune category 3). This is due to the concern of possible dissemination of live attenuated vaccine viruses. Varicella immunization is currently not recommended for the same reason.

26. Prevention of respiratory tract infections deserves attention. Influenza vaccine may be considered seasonally and repeated annually for children who are at least 6 months of age and are infected, or living with persons who are infected, with HIV. The use of conjugate *Haemophilus influenzae* type b vaccine and pneumococcal vaccine follows the recommendations for the general community. On the other hand, concern has been raised about the risk of disseminated BCG infection in HIV-infected infants immunised with BCG. In countries where the prevalence of tuberculosis is high, BCG vaccination for infants at birth should be a standard practice and this applies to asymptomatic HIV infected infants on a risk-benefit basis. BCG is recommended for all infants born to HIV-infected mothers in Hong Kong.

Nutrition

27. Breastfeeding by an HIV-infected mother carries a 16% excess risk of HIV infection for the infant and should be avoided. Wasting syndrome is a significant problem in HIV infected children, accounting for 17% of the reported AIDS-defining condition in the US in 1994. HIV-infected children require high-energy, high-protein, nutrient-dense diets. Depending on the child's ambulatory and clinical status, energy needs range from 75% to 150% of the recommended daily allowance (RDA) and protein needs should be between 100% and 150% of the RDA to support the immune system and avoid muscle wasting. (21) For early intervention, all infants and children diagnosed of HIV infection should receive a baseline nutritional assessment within 3 months of diagnosis with follow-up every 1 to 6 months depending on the child's status.

CARE OF ANTIRETROVIRAL EXPOSED, UNINFECTED CHILDREN

28. There are theoretical concerns of potential carcinogenicity of the nucleoside analogue antiretroviral drugs used in children postnatally and/or in utero exposure of ZDV or other antiretroviral agents. NRTIs may inhibit DNA polymerase gamma, a specific mitochondrial enzyme that controls mitochondrial DNA replication. In vitro, the NRTIs have demonstrated significant mitochondrial toxicity, with the eventual development of myopathy. ZDV use during pregnancy has also been associated with the development of mitochondrial toxicity among newborns. The concern for this and other yet unknown potential adverse effects have led clinicians to propose that children with antiretroviral exposure should be followed up into adulthood. (12) Long-

term follow-up should include annual physical examination; and for older adolescent females, gynaecologic evaluation with pap smears has been proposed by some experts. A mechanism to evaluate antiretroviral exposed children in Hong Kong should be considered.

Appendix

(The following tables have been adapted from tables and texts of the reports and manuscripts in the Reference List. A main source is reference number 4)

Table 1. Recommendations for PCP Prophylaxis and CD4+ Lymphocyte Monitoring for HIV-Exposed Infants and HIV-infected Children by Age and HIV Infection Status

| Age and HIV Infection Status | PCP Prophylaxis | CD4+ Monitoring |
|---------------------------------------|--|------------------------|
| Birth to 4-6 wk, HIV-exposed | None | 1 m of age |
| 4-6 wk to 4m, HIV-exposed | Prophylaxis | 3 m of age |
| 4-12 m, HIV-infected or indeterminate | Prophylaxis | 6,9 and 12 m of age |
| HIV infection reasonably excluded | None | None |
| 1-2 y, HIV-infected | Prophylaxis if CD4+ count < 750 cells/ μ L in first 12m or <500 cells/ μ L at 12-24m, or CD4+ percentage < 15% | Every 3-4 m |
| 2-5y, HIV-infected | Prophylaxis if CD4+ count < 500 cells/ μ L or CD4+ percentage < 15% | Every 3-4m |
| 6-12y, HIV-infected | Prophylaxis if CD4+ count <200 cells/ μ L or CD4+ percentage < 15% | Every 3-4 m |
| Any age, HIV-infected, prior PCP | Lifelong prophylaxis; refer to latest recommendation for adults with HIV infection | Every 3-4 m |

Table 2. Drug Regimens for PCP Prophylaxis for Children

| |
|---|
| Recommended regimen |
| TMP-SMX*, 150 mg/m ² /d (or 5 mg/kg/d) of trimethoprim with 750 mg/m ² /d (or 25 mg/kg/d) of sulfamethoxazole, divided BD PO, 3x/week on consecutive days |
| Acceptable alternative TMP-SMX dosage schedules |
| 150 mg/m ² /d of trimethoprim with 750 mg/m ² /d of sulfamethoxazole QD PO, 3x/week on consecutive days |
| 150 mg/m ² /d of trimethoprim with 750 mg/m ² /d of sulfamethoxazole, divided BD PO 7 days/week |
| 150 mg/m ² /d of trimethoprim with 750 mg/m ² /d of sulfamethoxazole, divided BD PO, 3x/week on alternate days |
| Alternative regimens when therapy with TMP-SMX is not tolerated* |
| Dapsone, 2mg/kg (not to exceed 100 mg), QD PO |
| Aerosolised pentamidine (for children ≥ 5y), 300 mg via Respirgard II inhaler, once a month |
| If neither dapsone nor aerosolized pentamidine is tolerated, some clinicians administer 4 mg/kg of pentamidine intravenously every 2 or 4 weeks |

♣ TMP-SMX indicates trimethoprim-sulfamethoxazole

* There is no official recommendation on children with G6PD deficiency

Table 3. Revised HIV Paediatric Classification System: Clinical Categories

| |
|---|
| Category N: Not Symptomatic |
| Children who have no signs or symptoms arising from HIV infection or who have only ONE of the conditions listed in Category A |
| Category A: Mildly Symptomatic |
| Children with ≥ 2 of the conditions listed below but none of the conditions listed in Categories B and C. |
| * Lymphadenopathy (>0.5 cm at > 2 site, bilateral =1 site) |
| * Hepatomegaly |
| * Dermatitis |
| * Parotitis |
| * Recurrent or persistent upper respiratory tract infection, sinusitis or otitis media |
| Category B: Moderately Symptomatic |
| Children who have symptomatic conditions other than those listed for Category A or C that are attributed to HIV infection. Examples of conditions in clinical Category B include, but are not limited to: |
| * Anaemia (<8 g/dL), neutropaenia ($<1000/\text{mm}^3$), or thrombocytopaenia ($< 100,000/\text{mm}^3$) persisting for ≥ 30 days |
| * Bacterial meningitis, pneumonia, or sepsis (single episode) |
| * Candidiasis, oropharyngeal (thrush) persisting >2 months in children > 6 months of age |
| * Cardiomyopathy |
| * Cytomegalovirus infection, with onset before 1 month of age |
| * Diarrhoea, recurrent or chronic |
| * Hepatitis |
| * Herpes simplex virus (HSV) stomatitis, recurrent (>2 episodes within 1 year) |
| * HSV bronchitis, pneumonitis, or oesophagitis with onset before 1 month of age |
| * Herpes zoster (shingles) involving ≥ 2 distinct episodes or more than 1 dermatome |
| * Leiomyosarcoma |
| * Lymphoid interstitial pneumonia (LIP) or pulmonary lymphoid hyperplasia complex |
| * Nephropathy |
| * Nocardiosis |
| * Persisting fever (lasting >1 month) |
| * Toxoplasmosis, onset before 1 month of age |
| * Varicella, disseminated |

| Category C: Severely Symptomatic |
|--|
| * Serious bacterial infections, multiple or recurrent (i.e., any combination of ≥ 2 culture-confirmed infections within a 2-year period) of the following types: septicaemia, pneumonia, meningitis, bone or joint infection, or abscess of an internal organ or body cavity (excluding otitis media, superficial skin or mucosal abscesses, and in-dwelling catheter-related infections). |
| * Candidiasis, oesophageal or pulmonary (bronchi, trachea, lungs) |
| * Coccidioidomycosis, disseminated (at site other than or in addition to lungs or cervical or hilar lymph nodes) |
| * Cryptococcosis, extrapulmonary |
| * Cryptosporidiosis or isosporiasis with diarrhoea persisting > 1 month |
| * Cytomegalovirus disease with onset of symptoms at age > 1 month (at a site other than liver, spleen or lymph nodes) |
| * Encephalopathy (\geq one of the following progressive findings present for ≥ 2 months in the absence of a concurrent illness other than HIV that could explain the findings): <ul style="list-style-type: none"> a) failure to attain or loss of developmental milestones or loss of intellectual ability, verified by standard development scale or neuropsychological test; b) impaired brain growth or acquired microcephaly demonstrated by head circumference measurements or brain atrophy demonstrated by computerised tomography or magnetic resonance imaging (serial imaging is required for children < 2 years of age); c) acquired symmetric motor deficit manifested by ≥ 2 of the following: paresis, pathologic reflexes, ataxia, or gait disturbance |
| * Infection with HSV causing a mucocutaneous ulcer that persists for > 1 month; or bronchitis, pneumonitis, or oesophagitis for any duration in a child > 1 month of age |
| * Histoplasmosis, disseminated (at a site other than or in addition to lungs or cervical or hilar lymph nodes) |
| * Kaposi's sarcoma |
| * Lymphoma, primary, in brain |
| * Lymphoma, small, noncleaved cell (Burkitt) or immunoblastic or large cell lymphoma of B-cell or unknown immunologic phenotype |
| * Mycobacterium tuberculosis, disseminated or extrapulmonary |
| * <i>Mycobacterium avium</i> complex or <i>Mycobacterium kansasii</i> , disseminated (at site other or in addition to lungs or cervical or hilar lymph nodes) |
| * <i>Pneumocystis carinii</i> pneumonia |
| * Progressive multifocal leukoencephalopathy |
| * Salmonella (nontyphoid) septicaemia, recurrent |
| * Toxoplasmosis of the brain with onset at > 1 month of age |
| * Wasting syndrome in the absence of a concurrent illness other than HIV infection that could explain the following findings: <ul style="list-style-type: none"> a) persistent weight loss $> 10\%$ of baseline, or b) downward crossing of at least one of the following percentile lines on the weight-for-age chart (e.g., 95th, 75th, 50th, 25th, 5th) in a child ≥ 1 year of age, or c) $< 5^{\text{th}}$ percentile on weight-for-age chart on 2 consecutive measurements, ≥ 30 days apart) plus 1) chronic diarrhea (at least 2 loose stools/day for ≥ 30 days) or, 2) documented fever (for ≥ 30 days, intermittent or constant) |

**Table 4. 1994 Revised Pediatric HIV Classification System:
Immunologic Categories Based on Age-specific CD4+ Lymphocyte
Count and Percentage**

| Immune Category | Age of Child | | |
|--|--------------------------|--------------------------|--------------------------|
| | ≤ 12 months | 1-5 years | 6-12 years |
| | Cell/mm ³ (%) | Cell/mm ³ (%) | Cell/mm ³ (%) |
| Category 1: No suppression | ≥ 1500 (≥ 25) | ≥ 1000 (≥25) | ≥ 500 (≥ 25) |
| Category 2: Moderate suppression | 750-1499 (15-24) | 500-999 (15-24) | 200-499 (15-24) |
| Category 3: Severe suppression | <750 (<15) | <500 (<15) | <200 (<15) |

Table 5. Characteristics of Nucleoside Analogue Reverse Transcriptase Inhibitors

| Generic Name | Zidovudine (ZDV/AZT) | Didanosine (ddI) | Zalcitabine (ddC) | Stavudine (d4T) | Lamivudine (3TC) | Abacavir (ABC) |
|----------------------|--|--|--|--|---|---|
| Trade Name | Retrovir | Videx | Hivid | Zerit | Epivir | Ziagen |
| Preparation | 100mg capsules 300 mg tablets 10 mg/ml IV solution 10 mg/ml oral solution | 25, 50, 100, 150, 200 mg chewable tablets 167, 250 mg sachets | 0.375, 0.75 mg tablets | 15,20,30,40 mg capsules 1mg/ml oral solution | 150 mg tablets 10 mg/ml oral solution | 300 mg tablets 20 mg/ml oral solution |
| Dose | <i>During labour and delivery:</i> Continuous IV infusion 2 mg/kg first hour, then 1 mg./kg until delivery <i>Neonatal:</i> 2 mg/kg Q6h <i>Paediatric:</i> 90-180 mg/m ² TDS or QID <i>Adult:</i> 200 mg TDS or 300 mg BD | <i>Neonatal:</i> 50 mg/m ² q12h <i>Paediatric:</i> 90-150 mg/m ² q12h <i>Adolescent/Adult:</i> ≥60 kg, 200 mg BD; < 60 kg 125 mg BD | <i>Neonatal:</i> unknown <i>Paediatric:</i> 0.005 to 0.01 mg/kg TDS <i>Adult:</i> 0.75 mg TDS | <i>Neonatal:</i> unknown <i>Paediatric:</i> 1 mg/kg BD <i>Adolescent/Adult:</i> < 60 kg, 30 mg BD; 60 mg, 40 mg BD | <i>Neonatal (<30 days):</i> (under study) 2 mg/kg BD <i>Paediatric:</i> 4 mg/kg BD <i>Adolescent/Adult:</i> < 50 kg, 2mg/kg BD; ≥ 50 kg, 150 mg BD | <i>Neonatal:</i> not approved for infants <3m. Infants 1-3m of age, 8 mg/kg BID under study <i>Paediatric/Adolescent:</i> 8 mg/kg BID, max 300 mg BID |
| Food Effect | No regard to meals | Take 1 hour before or 1 hour after meal | No regard to meals | No regard to meals | No regard to meals | No regard to meals |
| Toxic Effects | Anaemia, neutropaenia, headache Less frequently: myopathy, myositis, hepatitis | Gastro-intestinal upset. Less frequently: peripheral neuropathy, electrolyte disturbances Hyperuricaemia; Rarely: pancreatitis hepatitis, retinal depigmentation | Headache, fatigue; rarely peripheral neuropathy, pancreatitis hepatitis, skin rashes, oral and oesophageal ulcers, anaemia, neutropaenia | Headache, gastro-intestinal upset, skin rashes. Less frequently: peripheral neuropathy, pancreatitis, hepatitis | Headache, fatigue, gastro-intestinal upset, skin rashes. Less frequently: peripheral neuropathy, pancreatitis, hepatitis Neutropaenia | Nausea, vomiting, headache, fever, rash, anorexia, fatigue. Rarely potentially fatal hypersensitivity reaction, with fever, malaise, nausea, vomiting, diarrhoea and abdominal pain. Many have lymphadenopathy, ulceration of mucous membranes or rash. |

Adolescents should be dosed according to the Tanner Stage instead of chronologic age. Adolescents with Tanner Stage I and II should be dosed according to the pediatric age group while those with Tanner stage III and IV should use adult dosing. Careful monitoring of response and adverse effects is needed during this time of growth and change

Table 6. Characteristics of Non-nucleoside Reverse Transcriptase Inhibitors:

| Generic Name | Nevirapine | Delavirdine | Efavirenz |
|----------------------|--|--|---|
| Trade Name | Viramune | Rescriptor | Stocrin |
| Preparation | 200 mg tablets 10 mg/ml liquid (investigational) | 100 mg tablets | 50mg, 100 mg, 200 mg capsules |
| Dose | <i>Neonatal through 3 months</i> (under ACTG P365): 5 mg/kg qd for 14 days, then 120 mg/m ² q12h for 14 days, then 200 mg/m ² q12h. <i>Paediatric:</i> 120-200 mg/m ² q12h Start at 120 mg/m ² qd for the first 2 weeks and increase to BID full dose <i>Adolescent/Adult:</i> 200 mg q12h (initiate at half dose for the first 14 d) | <i>Neonatal and Paediatric:</i> unknown <i>Adolescent/Adult:</i> 400 mg TID | <i>Neonatal:</i> unknown <i>Paediatric:</i> (no data on appropriate dosage under 3 yrs of age) 10- <15 kg: 200 mg qhs; 15- <20 mg: 250 mg qhs; 20-<25 kg: 300 mg qhs; 25-<32.5 kg: 350 mg qhs; 32.5-<40 kg: 400 mg qhs; 40 kg: 600 mg qhs <i>Adolescent:</i> 600 mg qhs |
| Food Effect | Can be given with food | Can be taken with food | Can be taken with or without food, avoid high fat meal with drug |
| Toxic Effects | Skin rash, sedation, headache, gastrointestinal, rarely hepatitis | Skin rash, headache, fatigue, gastro-intestinal disturbances | Rash, CNS involvement(somnolence, insomnia, abnormal dreams, confusion, impaired concentration, agitation, hallucinations), elevated aminotransferase |

Adolescents should be dosed according to the Tanner Stage instead of chronologic age. Adolescents with Tanner Stage I and II should be dosed according to the paediatric age group while those with Tanner stage III and IV should use adult dosing. Careful monitoring of response and adverse effects is needed during this time of growth and change

Table 7. Characteristics of Protease Inhibitors:

| Generic Name | Nelfinavir | Indinavir | Ritonavir | Saquinavir | Amprenavir |
|----------------------|--|--|---|--|---|
| Trade Name | Viracept | Crixivan | Norvir | Invirase[hard gel], Fortovase [soft gel] | Agenerase |
| Preparation | 50mg/scoop powder 250 mg tablets | 200 mg, 400 mg capsules | 80 mg/ml liquid 100 mg capsules | 200 mg capsule | 15 mg/ml liquid 50 mg, 150 mg capsules |
| Dose | <i>Neonatal</i> (no data, under PACTG 353): 40 mg/kg BD <i>Paediatric</i> : 20-30 mg/kg TID but many experts give a higher dose: 55 mg/kg/dose BID to a maximum of 2 g/dose (exceeding the adult dose of 1.25 gm BID) <i>Adolescent/ Adult</i> : 750 mg TID or 1.25 gm BID | <i>Neonatal</i> : dose unknown, should not be given to neonates (hyperbilirubinaemia) <i>Paediatric</i> (under study): 500mg/m ² q8h. <i>Adolescent/ Adult</i> : 800 mg q8h | <i>Neonatal</i> : dose unknown <i>Paediatric</i> : 350-450 mg/m ² BID, start at 250 mg/m ² q 12h and increase stepwise over 5 days <i>Adolescent/ Adult</i> : 600 mg BID, start at 300 mg BID and increase to full dose over 5 days | <i>Neonatal and paediatric</i> : dose unknown <i>Adolescent/Adult</i> : 600 mg TID for HGC; 1200 mg TID for SGC | <i>Paediatric</i> : <u>Liquid formulation</u> : 4-12 and 13-16 yrs (if <50 kg): 22.5 mg/kg Bid or 17 mg/kg TID <u>Capsules</u> : 4-12 and 13-16 yrs (if <50 kg): 20 mg/kg BID or 15 mg/kg TID <i>Adult</i> : 1200 mg BID |
| Food Effect | Administer with meal or light snack | Empty stomach 1 hr before or 2 hrs after a meal (or taken with a light meal) | Food increases absorption | Administer within 2 hours of a full meal to increase absorption. Grapefruit juice increases absorption | Can be given with or without food |
| Toxic Effects | Diarrhea, abdominal pain, fatigue, rash, rarely hyperglycaemia and diabetes | GI disturbances, headache, asymptomatic hyperbilirubinaemia, less frequently: nephrolithiasis spontaneous bleeding episodes (hemophiliacs), hyperglycaemia, diabetes | GI disturbances, circumoral paraesthesia, hepatitis,, rarely spontaneous bleeding episodes in Hemophiliacs pancreatitis, increased triglycerides, cholesterol, hyperglycaemia, diabetes | GI disturbances, rarely spontaneous bleeding episodes (hemophiliacs), hyperglycemia, diabetes | GI disturbances, rash, paraesthesias, Stevens-Johnson syndrome (1%). Depression or mood disorder (15%), hyperglycemia, hypertriglyceridaemia, hypercholesterolaemia |

Adolescents should be dosed according to the Tanner Stage instead of chronologic age. Adolescents with Tanner Stage I and II should be dosed according to the paediatric age group while those with Tanner stage III and IV should use adult dosing. Careful monitoring of response and adverse effects is needed during this time of growth and change

Table 8. Combinations of Antiretroviral drugs for Use in Paediatric Settings

Frequently used initial combination therapies in paediatrics:

Zidovudine + lamivudine + nelfinavir or ritonavir
 Stavudine + didanosine + nelfinavir or ritonavir
 Stavudine + lamivudine + nelfinavir or ritonavir
 Zidovudine + lamivudine + nevirapine
 Stavudine + lamivudine + nevirapine
 Stavudine + didanosine + nevirapine
 Nelfinavir + nevirapine + zidovudine + lamivudine
 Nelfinavir + efavirenz + zidovudine + lamivudine

Regimens to be avoided due to overlapping toxicity or antagonistic antiviral effect:

Zidovudine + stavudine
 Didanosine + zalcitabine
 Stavudine + zalcitabine
 Zalcitabine + lamivudine
 Monotherapy

Currently licensed antiretroviral preparations in the USA for treatment of HIV infection. (All except for Delavirdine, Amprenavir and Lopinavir/ritonavir are registered in Hong Kong and these three drugs can be obtained by special arrangement).

| NRTI | NNRTI | PI |
|--------------------------|-------------|----------------------|
| Zidovudine (ZDV or AZT)* | Nevirapine* | Ritonavir* |
| Didanosine (ddI)* | Delavirdine | Nelfinavir* |
| Zalcitabine (ddC)* | Efavirenz | Indinavir |
| Lamivudine (3TC)* | | Saquinavir |
| Stavudine (d4T)* | | Amprenavir* |
| Abacavir (ABC)* | | Lopinavir/Ritonavir* |

NRTIs: Nucleoside analogue reverse transcriptase inhibitors

NNRTIs: Non-nucleoside analogue reverse transcriptase inhibitors

PIs: protease inhibitors

* paediatric formulations commercially available

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