GUIDELINES FOR HIV INFECTED AND EXPOSED CHILDREN

Introduction

The management of HIV disease in children is a shared responsibility of community physicians and pediatric HIV specialists. These guidelines focus on the role of pediatricians and family practitioners in the care they can offer to children who are HIV infected and to uninfected infants born to HIV infected mothers.

Community physician care

Providing primary health care for uninfected infants born to HIV infected mothers and to HIV infected children may include:

- following growth and development and providing childhood immunizations
- identifying the children at risk for HIV disease, confirming HIV status as early as possible to refer the infected child for specialized HIV care and treatment (Oak Tree Clinic, see contact below)
- providing primary care to an HIV infected child, ensuring full immunizations, providing education and psychosocial support to the family, treating minor infections early and refer to specialized pediatric HIV care

In all cases, communication with the pediatric HIV specialists is encouraged to optimize collaborative care.

Identifying children at risk for HIV disease

- Children born to newly diagnosed HIV infected women
- Immigrant children from HIV endemic areas
- Recent HIV diagnosis in a family member
- Adolescents with risk behavior (injection drug use, street involved, unprotected sex with an HIV+ partner) or a recent sexually transmitted disease
- Symptoms or signs such as lymphadenopathies, hepatomegaly, splenomegaly, severe bacterial infections, recurrent infections, parotitis, failure-to-thrive, recurrent or chronic diarrhea, dermatitis, unexplained prolonged fever, recurrent oral ulcers, hepatitis, LIP (lymphocytic interstitial pneumonitis), thrombocytopenia (ITP), encephalopathy (loss of milestones, developmental delay), opportunistic infections (PCP, TB, recurrent zoster, disseminated VZV) etc.

Some HIV infected children are slow progressors and may appear asymptomatic for many years.

CARE OF HIV EXPOSED UNINFECTED CHILDREN

Guidelines for perinatal care, including management algorithms, treatment recommendations summaries and prescribers' orders for obstetrical, intra-partum and infant management are available at: http://cfenet.ubc.ca/therapeutic-guidelines/pregnant-women and www.bcwomens.ca/Services/HealthServices/OakTreeClinic/ClinicalGuidelines.htm

Infant antiretroviral prophylaxis

All HIV exposed infants should be offered antiretroviral prophylaxis regardless of maternal antenatal or intrapartum antiretroviral therapy, viral load, or mode of delivery. The recommended regimen will depend on the presumed level of risk:

- Infants born to an HIV infected mother who took combination antiretroviral therapy (cART) in pregnancy and has a viral load <1000 copies/mL near delivery are offered oral zidovudine for six weeks.
- Infants born to an HIV infected mother who has a known or projected viral load >1000 copies/mL or who did not receive antepartum antiretroviral therapy should receive a 3-drug combination antiretroviral regimen for the first 2 weeks of life, followed by zidovudine until 6 weeks of age.
- For mothers with unknown HIV status at delivery, a rapid (point-of-care) HIV antibody test is recommended where available. Starting the infant on a 3-drug regimen is recommended until maternal HIV test results are available, unless the mother's rapid HIV test is non-reactive at delivery and exposure in the last 3 weeks can be reasonably ruled out. In situations where high risk behaviour (and potential HIV exposure) is suspected close to delivery, maternal status can best be determined by an HIV-PCR (NAT) test at delivery and repeating the test 7-12 days post-partum. It is essential to promptly obtain the results of maternal HIV testing in order to discontinue infant prophylaxis in a timely manner when the mother is confirmed HIV uninfected.

  The window period between the time of last exposure and the detection of infection has been shortened with the current assays, to an average of 3 weeks for serologic assays (Ab, EIA) and 7-12 days for virologic assays (HIV PCR or NAT).

Formula feeding

Exclusive formula feeding is recommended to reduce the risk of HIV transmission, regardless of maternal antiretroviral therapy and viral load. In BC, infant formula is available free of charge for the first year of life to infants born to HIV infected mothers living with their mother, through a provincially funded program. Applications to the program are facilitated through the Oak Tree Clinic at BC Women's Hospital and Health Centre.

Infant laboratory tests

Infants exposed to HIV should be tested for HIV infection using a virologic test (HIV-PCR / NAT) at birth, 4 weeks and 3 - 4 months of age. HIV specialists may recommend additional testing for infants at high risk of vertical transmission. The BC Centre for Disease Control laboratories currently uses an HIV RNA PCR test for diagnostic purposes.

If the HIV PCR is reactive, a confirmatory PCR test and HIV viral load should be requested immediately on another sample. When an infant is found to be HIV-infected, antiretroviral prophylaxis should be discontinued and an immediate referral to an HIV specialist should be made for comprehensive HIV care and therapy initiation. This can be arranged by phoning the Oak Tree Clinic.

HIV infection can be excluded when two HIV PCR tests are non-reactive, one collected after 4 weeks of age and the other at least 4 weeks after the end of prophylactic antiretrovirals. ***Serologic (Ab, EIA) tests are not indicative of infant status*** due to the presence of detectable maternal HIV antibodies up to 18-24 months of age. A confirmatory HIV Ab test is recommended to document seroreversion after 18 months of age.

Infants should also be monitored with a complete and differential blood count at 4 weeks of age. Anemia or neutropenia are not uncommon after 4 weeks of zidovudine, while platelet levels are generally elevated. If hemoglobin levels drop below 100 g/l and are expected to further decrease with continued zidovudine exposure, early discontinuation of zidovudine prophylaxis at 4 weeks is to be considered. If an infant presents with unexplained neurologic or gastro-intestinal symptoms, mitochondrial toxicity, although rare, should be suspected and liver function tests and lactate level should be measured.

Management of HIV exposed infants born in BC is offered through the Oak Tree Clinic at BC Women's Hospital and Health Centre. ***In addition, registration of mother-infant pairs with the provincial and national surveillance programs is facilitated through the clinic.***

Infant follow up

Infants born to HIV infected mothers are considered vulnerable and require diligent follow-up in order to reach their full health potential. Studies have shown higher incidences of severe infections in HIV exposed uninfected infants, the causes of which are yet unclear.

Factors such as poverty, food insecurity, low literacy, inexperience in parenting and parental substance or alcohol use put infants at higher risk for failure-to-thrive, developmental delay, behavioral disorders, neglect, abuse, etc. Family physicians and pediatricians play an essential role in identifying and addressing such issues in HIV exposed uninfected infants and children. They can facilitate specialist referrals and access to resources for the children who need them. Communications with public health nurses, immunization clinics, the Infant

Development Program (IDP), Sunny Hill Health Centre for Children, BC Centre for Abilities, the Ministry of Children and Families (MCFD) and the Vancouver Aboriginal Child and Family Services Society (VAC-FSS) are important for the well-being of these children.

Long term follow up of HIV exposed, uninfected children who were exposed to antiretrovirals in the perinatal period is generally recommended into adulthood, due to theoretical concerns regarding the potential for carcinogenicity of nucleoside analogue ARV drugs. At the Oak Tree Clinic, visits are typically scheduled at 2, 4 and 6 weeks, 3, 6, 9, 12 and 18 months. A yearly visit is recommended thereafter at least until age 5.

Immunizations
HIV exposed infants and children should receive all routine immunizations. Updated schedules are available at **immunizebc.ca**

Contacts and references
Oak Tree Clinic personnel (reception 604-875-2212, nurse clinician 604-875-2250) are available to provide telephone advice regarding HIV positive or at risk pregnant women and their infants. After hours and on weekends, contact Children's and Women's Health Centre of BC (604-875-2161) and ask for the perinatologist on call for obstetric issues and pediatric infectious diseases specialist on call for pediatric issues.

CARE OF HIV INFECTED CHILDREN

Guidelines are available at http://www.aidsinfo.nih.gov/ (US guidelines), http://www.who.int/publications/guidelines/hiv_aids/en/index.html (WHO guidelines) and at www.pentatrials.org (European guidelines)

Primary care
Primary care is essential to maintain the health of HIV infected children, including optimal nutrition and up-to-date immunizations. Ensuring optimum calcium and vitamin D intake and encouraging weight bearing exercise as for all children is important.

Immunizations
HIV infected children should receive all immunizations according to the provincial schedule. The only exceptions are severely immuno-compromised children (CD4 fraction <15%, see Table 2.) who should not receive live vaccines (MMR, VZV). Live vaccines can be administered safely after immune recovery following antiretroviral therapy. A pediatric HIV specialist can advise in those cases.
To view the updated provincial immunization schedule, go to **immunizebc**.ca

HIV care
Children with HIV should have access to an interdisciplinary care team, and receive medical care by clinicians experienced in the management of pediatric HIV. In BC the pediatric HIV tertiary care facility is located at the Oak Tree Clinic at Women's Hospital and Health Centre in Vancouver. The clinic provides family centered HIV care and treatment to HIV positive women, pregnant women and their children. The medical team includes physicians with HIV expertise in pediatrics, internal medicine, obstetrics/gynecology and mental health, nurse clinicians, nurse practitioners, pharmacists, dietitians, social workers, counselors and outreach workers. Participation in research studies is offered through the research team.

Antiretroviral therapy for HIV infected children
The goals of treatment with antiretroviral (ARV) drugs in HIV-infected children are to achieve and sustain full viral load (VL) suppression and minimize short- and long-term ARV drug toxicity. Sustained VL suppression dramatically decreases HIV-related morbidity and mortality, improves growth and development, preserves immune function and prevents the emergence of drug resistance. A high adherence level of >95% of prescribed doses is targeted to maintain viral suppression.
Antiretrovirals are available for children through the BC Centre for Excellence in HIV/AIDS (CfE), in consultation with a pediatric HIV specialist.

Baseline investigations
Children should be examined for opportunistic infections (OIs) and complications of HIV, and their growth and neurodevelopment should be assessed. Baseline pre-antiretroviral therapy investigations should include HIV RNA VL, CD4 cell count and percentage, testing for other blood-borne infections (especially hepatitis A, B and C), hematology and biochemistry profiles, HIV resistance genotype and HLA-B*5701 genotype (to predict Abacavir sensitivity). Because normal absolute CD4 counts are higher in infants and young children than in adults (Table 2), percentages are generally preferred in children younger than 6 years.
A chest radiograph is recommended at baseline. Assessment for tuberculosis infection (latent or active) is recommended for newly arrived immigrant or adopted children from endemic countries, and should be considered for Aboriginal children.

Monitoring
Clinical monitoring and measurement of CD4 and VL should be repeated every 3 months in children who are clinically stable, whether on therapy or not, and more frequently in infants ≤12 months and in older children approaching treatment thresholds, or following initiation or change of therapy.

After initiation or change of therapy, weekly or bi-weekly visits or phone calls are scheduled to assess tolerability and adherence to medications until stability is

reached. Monitoring for short and long term toxicities is recommended every 3 months with hematology, hepatic, pancreatic and renal function tests. Additional investigations are recommended for children taking specific antiretroviral agents (for example, urine ACR and serum phosphate for children on Tenofovir). Fasting glycemia and lipid profile are recommended at baseline and once a year for children age ≥10.

While evidence is limited, there is some concern that HIV infected children may be at risk for not attaining their expected peak bone mass. Ensuring optimum calcium and vitamin D intake and encouraging weight bearing exercise as for all children is important. Although there are currently no reliable methods to predict bone fragility in children, monitoring by DXA scan should be considered starting at age 16, especially for youth exposed to Tenofovir for more than 3 years.

See **Table 1** for schedule of follow-up.

Indications for initiation of antiretroviral therapy in children

Infants <12 months

Treat *all* infants regardless of clinical symptoms, immune status or viral load.
All HIV infected infants <12 months should also receive cotrimoxazole (TMP-SMX) for *Pneumocystis jiroveci* (formerly *carinii*) pneumonia (PCP) prophylaxis, ***regardless of CD4 count***. Immediate life-long treatment of infants has been shown beneficial in terms of AIDS-free survival and neurodevelopmental outcomes. Therefore, in young children who started treatment before 12 months of age, treatment should generally be continued. However, under exceptional circumstances a treatment interruption can be considered with close monitoring of clinical, immune and viral load parameters by an HIV specialist and prompt re-initiation of treatment when indicated.

Children aged ≥1 year

In accordance with the US and European guidelines, we recommend treating HIV-infected children according to their clinical and immune status:

- Treat all children with AIDS or significant symptoms (clinical category C or most clinical category B conditions)

Treat children with minimal or no symptoms (clinical categories N and A, or single episode of bacterial infection) according to their CD4 values:

- 1 to <3 years: CD4 <1000 cells/mm^3 or <25%
- ≥3 to <5 years: CD4 <750 cells/mm^3 or <25%
- ≥5 years: CD4 ≤500 cells/mm3

Treatment is also recommended in children with HIV RNA levels >100,000 copies/mL regardless of symptoms or CD4 count.

The revised 2013 WHO guidelines recommend starting treatment in all children under 5, however these are aimed at resource-limited settings where close monitoring of CD4 and viral load may not be readily available.

We recommend to ***consider all children for treatment***, even those with minimal or no symptoms and CD4 counts higher than the above thresholds. On a case-by-case basis, providers may elect to defer therapy based on clinical and/or psychosocial factors.

Prior to starting therapy, the ability of the patient and caregiver to adhere to therapy regimen needs to be addressed, including:

- Age of the child and formulation of drug that will be tolerated
    - Some ARVs are available as liquids or chewable tablets
    - Some tablets can be split, crushed and mixed with food
- Schedule to fit with activity and meal schedule
    - Once daily regimens are favored for adolescents
    - Some agents need to be taken with a meal
- Pill burden
    - Co-formulated tablets exist that minimize pill burden
- Specific drug side effects
    - GI upset, sleep disturbances and neurologic effects, benign jaundice etc.
- Contraception plans should always be addressed with adolescents
    - Drug interactions between oral contraceptives and ARVs can decrease efficacy of contraceptives.
    - Efavirenz is not recommended in young women who do not use contraception.

Initial therapy for HIV infected children

Combination antiretroviral therapy or cART is prescribed as at least 3 drugs of at least 2 different classes – two nucleoside reverse transcriptase inhibitors (NRTI) and either a protease inhibitor (PI) or a non-nucleoside reverse transcriptase inhibitor (NNRTI)

Factors to consider when choosing a first regimen include:

- Patient and family readiness to start therapy
- Age of the child
- Ability to swallow tablets or capsules
- Weight and height (doses are calculated according to age, weight or body surface area depending on the agent)
- Schedule (most pediatric regimens require twice daily administration)
- HLA-B*5701 as predictor of abacavir hypersensitivity
- Baseline resistance genotype

Preferred regimens

- NNRTI-based:
  - Two NRTI plus nevirapine (children < 3 years)
  - Two NRTI plus efavirenz (children ≥ 3 years)
- PI-based
  - Two NRTI plus lopinavir / ritonavir (children ≥14 days and ≥42 weeks gestational age equivalent)
  - Two NRTI plus atazanavir / ritonavir (children ≥ 6 years)

NRTI backbone combinations

- Zidovudine plus lamivudine (available as Combivir for older children)
- Abacavir plus lamivudine (available as Kivexa for older children). Do not use abacavir in HLA-B*5701 positive individuals
- Tenofovir plus lamivudine (or tenofovir plus FTC combined as Truvada for older children). Tenofovir is not recommended in pre-pubertal children (Tanner stage ≤ 3) due to its potential effects on bone mineralization.

Adverse drug effects

Types of adverse drug effects include:

- Bone marrow suppression, most common with zidovudine. These effects can be exacerbated with TMP-SMX. Increased mean corpuscular volume (MCV) and elevated platelet count are common in children on zidovudine
- Allergic reactions such as skin rashes and hypersensitivity reactions can happen with any agent but are more common with NNRTI drugs and may be associated with hepatic toxicity. Nevirapine may cause Stevens-Johnson Syndrome and require immediate drug discontinuation
- Abacavir, an NRTI, can cause potentially fatal hypersensitivity reactions and should not be prescribed to HLA B5701 carriers. The risk is extremely low in individuals who do not carry the HLA B*5701 allele. The drug should never be restarted if a reaction occurs
- Neurologic effects such as vivid dreams, sleep disturbances and decreased ability to focus are common with Efavirenz
- Benign unconjugated hyperbilirubinemia and jaundice are common with Atazanavir, which also rarely causes kidney stones
- Decreased renal function: Tenofovir can affect the proximal tubule (Fanconi-type syndrome). Urine ACR (microalbumin creatinine ratio) and serum phosphate levels should be monitored every 3 months
- Tenofovir is not recommended in pre-pubertal children due to concerns of potential bone demineralization
- Mitochondrial dysfunction, manifesting as lactic acidosis, hepatic toxicity, pancreatitis and peripheral neuropathy, primarily seen with NRTI drugs. Serum lactate levels are not routinely recommended in asymptomatic children
- Lipodystrophy and metabolic abnormalities, including body fat redistribution (lipoatrophy of the face and limbs, lipohypertrophy of the abdomen, dorso-cervical pad), hyperlipidemia, insulin resistance, diabetes

mellitus. These are primarily seen with prolonged use of NRTI and PI agents. An annual fasting lipid profile is recommended for children starting at age 10

Detailed information about specific adverse reactions and management available at www.aidsinfo.nih.gov

In case of toxicity or intolerance:

- Severe or life threatening: discontinue all drugs and resume after symptoms have resolved with substitution of the responsible drug
- Moderate: continue therapy and substitute offending drug
- Mild: continue therapy; substitution may not be necessary
- Dose reduction is never recommended as it leads to emergence of resistance. It is rarely done in special circumstances when therapeutic drug monitoring has been performed.
- Single drug substitution is permissible in case of toxicity or intolerance
- Due to the very long half life of NNRTI, in case of discontinuation of Nevirapine or Efavirenz, it is recommended to continue the other ARVs for an additional 7-10 days to avoid the emergence of resistance.

Changing antiretroviral therapy

When virologic suppression cannot be achieved (viral load remains detectable after at least 6 months of therapy) or in case of virologic rebound (increase in viral load after initial response), adherence and genotypic viral resistance should be assessed before a regimen switch is considered. Sustained viral load suppression can preserve or restore immunologic function (CD4), prevent disease progression and prevent development of additional drug resistance. Note: a “blip” in viral load (< 250 copies/mL) may not be significant if seen in isolation with subsequent undetectable viral loads.

Collaboration with a pediatric HIV specialist is recommended to

- Assess adherence to therapy and address barriers, develop strategies to improve adherence
- Assess medication intolerance
- Assess medication doses, interactions with other medications, factors affecting drug absorption and metabolism
- Perform ARV drug-resistance testing

Choosing a new antiretroviral regimen

- Resistance testing is essential in choosing a new regimen, as well as results of previous resistance testing and history of all ARVs taken in the past. Resistance testing is more informative when performed on a sample collected while the patient was taking the failing regimen; it can be done retrospectively on a stored sample.
- When changing therapy because of toxicity or intolerance, choose agents

with different toxicity and side-effect profiles. Change of a single drug in a multi-drug regimen is permissible. Intolerance in the distant past does not preclude re-challenging under controlled circumstances (except abacavir).

- When changing therapy because of treatment failure, adherence to therapy should be assessed as a primary cause of failure.
- The new regimen should include at least three drugs including at least two fully active agents. Potential cross resistance between drugs should be considered, as well as future implications of a given change in therapy.
- A viral tropism assay should be requested when the use of a CCR5 antagonist (Maraviroc) is being considered.
- As new agents are becoming available for children and adolescents, consultation with a specialist in pediatric HIV infection is recommended.

Prophylaxis against opportunistic infections

Pneumocystis pneumonia (PCP)

Indications:

- all HIV infected infants starting at 4-6 weeks of age until 12 months of age (regardless of CD4 count)
- all HIV infected children with low age-adjusted CD4 count:
  ≤500 cells/mm^3 or ≤15% fraction for children 1 to 5 years of age
  ≤200 cells/mm^3 or ≤15% fraction for children > 6 years of age
- consider prophylaxis for any HIV infected child who has a rapid decline in CD4 count or has symptomatic HIV disease regardless of the CD4 count
- secondary prophylaxis in any child with a previous episode of PCP should be discussed with a pediatric HIV specialist.

Regimens:

TMP-SMX: 150 mg/m^2 body surface area TMP and 750 mg/m^2 body surface area SMX (maximum dose 320 mg TMP/1600 mg SMX) per day given orally as:

- 2 divided doses or a single daily dose administered on three consecutive days per week *or*
- 2 divided doses administered daily (7 days per week) *or*
- 2 divided doses administered three times per week on alternate days.

In the case of sulfonamide allergy, desensitization to TMP-SMX may occasionally be considered. Children should be referred to a pediatric HIV centre if they are intolerant to TMP-SMX.
Alternatives in case TMP-SMX intolerance include dapsone or atovaquone.
Aerosolized pentamidine 300 mg once monthly using Respirgard II inhaler can be used in special circumstances (children aged ≥ 5 years).

Other prophylactic interventions for children with severe immune suppression are available at www.aidsinfo.nih.org and should be discussed with a pediatric HIV consultant.

Disclosure of HIV diagnosis to children

HIV infected children have a right to know the reason for their medications, clinic visits and blood collections. It is recommended to start the disclosure process at an early age, using age-appropriate concepts and language, and building up as the child matures. Disclosure should be done with the parents' or caregivers' consent, preferably initiated by them at home around age 6 to 8, with follow-up during clinic visits. Using available educational material is recommended to address issues such as general health, the immune system, the HIV virus, CD4 counts and viral load, viral resistance, adherence etc. Timely disclosure helps maintain a trusting relationship between the child, the parents or caregivers and the health care team. All children should be fully aware of their HIV condition before adolescence, and empowered to participate in their own care as soon as possible.

Specific issues for adolescents

Medication adherence is a particular challenge for adolescents. Minimizing pill burden, choosing a once-daily regimen and discussing individualized strategies may improve chances of adherence. Increasing the frequency of contacts with the health care providers, including by phone calls or text messaging may also help support adherence.

Safer sexual practices should be reviewed periodically with adolescents, for the prevention of sexually transmitted diseases and to avoid transmission of HIV to partners.

Disclosure of HIV status to sexual partners should also be discussed and reviewed periodically, including personal and legal implications. Optimal ARV adherence to maintain an undetectable viral load and using condoms for penetrative sex are strongly recommended. For updated information on HIV criminal law, visit www.aidslaw.ca/criminallaw/

Effective contraception should be offered and contraceptive options discussed individually, taking into account interactions between ARVs and hormonal contraceptives. ARV regimens for young women of reproductive age should preferably not contain efavirenz, due to its potential teratogenicity.

Young adults should be prepared early for a smooth transition from pediatric to adult care around 17 to 22 years of age. Close collaboration and communication with an adult HIV team offering interdisciplinary care may ease the transition process and continuity of care. A comprehensive transition policy is being developed in BC. Youth cared for at the Oak Tree Clinic are offered a choice to

continue receiving their HIV care at the Oak Tree Clinic (switching from pediatric to adult ID specialist) or to transition to another specialized HIV provider in their area of the Province.

Table 1: Schedule of Care for HIV Infected Infants and Children[1]

Procedure	Frequency				
	Initial work-up	1 month after starting or switching ARVs	Every 3 months	Every 6 months	Yearly
History and examination	X	X	X		
Developmental assessment	X			if ≤ 3 yrs	if > 3 yrs
Hematology panel	X	X	X		
Kidney & liver function tests[2]	X	X	X		
Fasting lipids[3]/glucose					X
Urinalysis	X				as needed[4]
CD4 count and %[5]	X	X	X		
HIV viral load	X	X	X		
HLA-B*5701	X				
HIV genotype	X				as needed
Chest X-ray	X				as needed
Other serology[6]	X				X
Ophthalmology[7]	X				as needed
Cardiology	X				X
Bone health assessment[8]					X
Testing for latent tuberculosis[9]	X				as needed

1. More frequent evaluations may be necessary in children with advanced immune disease.
2. Additional investigations while on antiretroviral therapy include creatinine kinase and amylase; also include serum calcium, phosphate and urine microalbumin/creatinine ratio (ACR) if on Tenofovir.
3. Fasting lipids if on ARV include triglycerides, cholesterol, HDL, LDL.
4. If taking Tenofovir
5. More frequent if rapidly decreasing or severely immunosuppressed
6. Hepatitis A, B, C, Epstein Barr virus, toxoplasmosis, cytomegalovirus, herpes simplex virus, varicella zoster virus, measles, mumps, and rubella.

7. CMV infected and severely immunosuppressed patients may require eye examination every 4 to 6 months.
8. Bone health: dietary assessment in all children, consider serum 25-OH-vitamin D, DXA scans in children ≥ 16 years of age.
9. For children at risk, including immigrant and adopted children from endemic countries and Aboriginal children.

Table 2: Immunological Categories for HIV-Infected Children by Age-Specific CD4 count (cells/mm^3) and CD4 percentage

Immunologic Category	CD4 count By Age of Child			CD4%
	< 12 months	1-5 years	6-12 years	All ages
No immune suppression	> 1500	> 1000	> 500	> 25%
Moderate suppression	750 - 1500	500 - 1000	200 - 500	15 – 25%
Severe suppression	< 750	< 500	< 200	< 15%

Reference: 1994 revised classification system for HIV in children. MMWR1994;43.(RR12). See www.aidsinfo.nih.gov

Table 3: Antiretroviral Drug Dosing for Children

See www.aidsinfo.nih.gov for detailed information on all ARVs. For each medication, the exact formulation will vary by child's weight, ability to take pills, and tablet sizes available. Consult with a pharmacist with experience in pediatric HIV for guidance.

Generic name, abbreviation	Recommended Dose and Special Instructions	Dosage forms	Comments
Nucleoside/tide Reverse Transcriptase Inhibitors (NRTI)			
Abacavir (ABC)	For children ≥3 months of age ▪ 8 mg/kg PO twice daily ▪ Maximum 300 mg PO twice daily ▪ If clinically stable with an undetectable viral load and stable CD4 count for at least 24 weeks, may consider ABC 16 – 20 mg/kg/day given PO once daily to a maximum of 600 mg daily	▪ 20 mg/mL oral solution (strawberry banana flavor) ▪ 300 mg oral tablet	Avoid if HLA-B*5701 positive.

<table>
<tr><th>Generic name, abbreviation</th><th>Recommended Dose and Special Instructions</th><th>Dosage forms</th><th>Comments</th></tr>
<tr><td>Lamivudine (3TC)</td><td>▪ Age <30 days: 2 mg/kg/dose PO twice daily
▪ Age ≥30 days: 4 mg/kg/dose PO twice daily
▪ Maximum 150 mg PO twice daily</td><td>▪ 10 mg/mL oral solution (strawberry-banana flavor)
▪ 150 mg, 300 mg oral tablets</td><td>For dosing of 3TC for the prevention of vertical transmission – see Pregnant Women Therapeutic Guideline http://cfenet.ubc.ca/therapeutic-guidelines/pregnant-women</td></tr>
<tr><td>Tenofovir (TDF)</td><td>For children ≥2 years of age
▪ 8 mg/kg PO once daily
▪ Maximum 300 mg PO once daily</td><td>▪ 300 mg oral tablet</td><td>Not recommended first-line in pre-pubertal children

Caution if concomitant nephrotoxic drugs</td></tr>
<tr><td>Zidovudine (ZDV, AZT)</td><td>For children ≥4 weeks of age:
<table>
<tr><th>Body Weight (kg)</th><th>Dose (mg/dose)</th><th>Dose frequency</th></tr>
<tr><td>4 to <9</td><td>12 mg/kg</td><td>Twice daily</td></tr>
<tr><td>≥9 to <30</td><td>9 mg/kg</td><td>Twice daily</td></tr>
<tr><td>≥30</td><td>300 mg</td><td>Twice daily</td></tr>
</table>
▪ Maximum 300 mg PO twice daily</td><td>▪ 10 mg/mL IV solution
▪ 10 mg/mL oral syrup (strawberry flavour)
▪ 100 mg oral capsule (capsules may be opened)</td><td>For dosing of ZDV for the prevention of vertical transmission – see Pregnant Women Therapeutic Guideline http://cfenet.ubc.ca/therapeutic-guidelines/pregnant-women</td></tr>
<tr><td colspan="4">NRTI combination formulations</td></tr>
<tr><td>Tenofovir-Emtricitabine (TDF/FTC) - Truvada®</td><td>1 tablet PO daily
Refer to TDF dosing above</td><td>Fixed-dose combination tablet: 300 mg TDF / 200 mg FTC</td><td>Not recommended first-line in pre-pubertal children.

Caution if concomitant nephrotoxic drugs</td></tr>
<tr><td>Abacavir-Lamivudine (ABC/3TC) - Kivexa®</td><td>1 tablet PO daily
Refer to ABC and 3TC dosing above</td><td>Fixed-dose combination tablet: 600 mg ABC / 300 mg 3TC</td><td>Avoid if HLA-B*5701 positive</td></tr>
</table>

<table>
<tr><th colspan="4">Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTI)</th></tr>
<tr>
<td>Efavirenz (EFV)</td>
<td>For children ≥3 years of age and weight ≥10kg:
<table>
<tr><th>Body Weight (kg)</th><th>Dose (mg/dose)</th><th>Dose frequency</th></tr>
<tr><td>10 to <15</td><td>200 mg</td><td>daily</td></tr>
<tr><td>15 to <20</td><td>250 mg</td><td>daily</td></tr>
<tr><td>20 to <25</td><td>300 mg</td><td>daily</td></tr>
<tr><td>25 to <32.5</td><td>350 mg</td><td>daily</td></tr>
<tr><td>32.5 to <40</td><td>400 mg</td><td>daily</td></tr>
<tr><td>≥40</td><td>600 mg</td><td>daily</td></tr>
</table>
</td>
<td>▪ 50 mg, 100 mg, 200 mg, 600 mg oral capsules (capsules may be opened)

▪ Suspension available via Expanded Access (strawberry-mint flavor)</td>
<td>Give at bedtime

Give on an empty stomach to decrease side effects

Interacts with CYP P450 metabolized drugs</td>
</tr>
<tr>
<td>Nevirapine (NVP)</td>
<td>Lead-in period required to minimize adverse effects

For children ≥15 days to < 8 years of age:
▪ 200 mg/m^2/dose PO once daily for 14 days then increase to 200 mg/m^2/dose PO twice daily
▪ Maximum 200 mg PO twice daily

For children ≥ 8 years of age:
▪ 120 – 150 mg/m^2/dose PO once daily for 14 days then increase to 120 – 150 mg/ m^2/dose PO twice daily
▪ Maximum 200 mg PO twice daily

Pediatric Dose Extended Release Formulation: only for children ≥ 6 years of age
▪ Children receiving NVP 200 mg IR tabs PO twice daily can be switched to 400 mg XR tab PO once daily without a lead in
▪ Children not already receiving NVP (who will be receiving the weight appropriate dose of 400 mg/day) should be initiated with 200 mg IR tab once daily x 14 days as a lead in dose and then can be switched to 400 mg XR tab once daily</td>
<td>▪ 200 mg oral immediate release tablet (IR tablet may be crushed)

▪ 400 mg oral extended-release tablet (XR tablet must be swallowed whole; must not be chewed, crushed or divided) *only for children ≥ 6 years

▪ Suspension (10 mg/mL) available via Expanded Access</td>
<td>For dosing of NVP for the prevention of vertical transmission – see Pregnant Women Therapeutic Guideline http://cfenet.ubc.ca/therapeutic-guidelines/pregnant-women

Interacts with CYP P450 metabolized drugs</td>
</tr>
<tr>
<td>Rilpivirine (RPV)</td>
<td>Age ≥ 18 years: 25 mg PO once daily

Safety and efficacy in pediatric patients has not been established. Not approved or recommended for use in</td>
<td>▪ 25 mg oral tablet</td>
<td>Give with a meal of at least 500 calories

Metabolized by CYP P450 3A

Avoid concomitant</td>
</tr>
</table>

<table>
<tr><td></td><td>children < 18 years</td><td></td><td>administration with proton-pump inhibitors</td></tr>
<tr><td>Etravirine (ETR)</td><td>For children > 6 years of age and weighing ≥16 kg
<table><tr><th>Body Weight (kg)</th><th>Dose (mg/dose)</th><th>Dose frequency</th></tr><tr><td>16 to <20</td><td>100 mg</td><td>Twice daily</td></tr><tr><td>20 to <25</td><td>125 mg</td><td>Twice daily</td></tr><tr><td>20 to <30</td><td>150 mg</td><td>Twice daily</td></tr><tr><td>≥30</td><td>200 mg</td><td>Twice daily</td></tr></table></td><td>▪ 100 mg, 200 mg oral tablet (tablet may be dispersed in water for immediate ingestion)</td><td>Give with food

Interacts with CYP P450 metabolized drugs</td></tr>
</table>

<table>
<tr><th colspan="4">Protease Inhibitors (PI)</th></tr>
<tr><td>Atazanavir (ATV)

give with boosted dose Ritonavir (RTV)</td><td>For children age ≥ 6 years of age:
<table><tr><th>Body Weight (kg)</th><th>ATV / RTV Dose (mg/dose)</th><th>Dose frequency</th></tr><tr><td>15 to <20</td><td>ATV 150 mg</td><td>once daily</td></tr><tr><td></td><td>RTV 100 mg</td><td>once daily</td></tr><tr><td>20 to < 40*</td><td>ATV 200 mg*</td><td>once daily</td></tr><tr><td></td><td>RTV 100 mg</td><td>once daily</td></tr><tr><td>≥ 40</td><td>ATV 300 mg</td><td>once daily</td></tr><tr><td></td><td>RTV 100 mg</td><td>once daily</td></tr></table>*To avoid underdosing in children weighing ≥ 35 kg, particularly if also taking tenofovir – may increase dose to ATV 300 mg once daily
▪ Maximum ATV 300 mg PO daily and RTV 100 mg PO daily</td><td>Atazanavir available as:
▪ 150 mg, 200 mg, 300 mg capsules (capsules may be opened, mixed with applesauce for immediate ingestion with light meal)

Ritonavir available as:
▪ 100mg tablet
▪ 80 mg/mL oral solution (poor palatability with bad aftertaste)</td><td>Give with food

Interacts with CYP P450 metabolized drugs

Avoid concomitant administration with proton-pump inhibitors, H2 blockers, antacids</td></tr>
<tr><td>Darunavir (DRV)

give with boosted dose Ritonavir (RTV)</td><td>For treatment experienced children ≥ 3 years of age who weigh ≥ 10 kg and for treatment naive adolescents ≥ 12 years of age:
<table><tr><th>Body Weight (kg)</th><th>Dose (mg/dose)</th><th>Dose frequency</th></tr><tr><td>≥10 to <13</td><td>DRV 225 mg</td><td>twice daily</td></tr></table></td><td>Darunavir available as:
▪ 75 mg, 150 mg, 400 mg, 600 mg, 800 mg tablets
▪ 100 mg/mL oral suspension (also contains 80 mg/mL ritonavir) available in US and Europe only</td><td>Give with food

Interacts with CYP P450 metabolized drugs</td></tr>
</table>

<table>
<tr>
<td></td>
<td>
<table>
<tr><td></td><td>RTV 32 mg</td><td>twice daily</td></tr>
<tr><td>≥13 to <15</td><td>DRV 300 mg</td><td>twice daily</td></tr>
<tr><td></td><td>RTV 40 mg</td><td>twice daily</td></tr>
<tr><td>≥15 to <30</td><td>DRV 375 mg</td><td>twice daily</td></tr>
<tr><td></td><td>RTV 50 mg</td><td>twice daily</td></tr>
<tr><td>≥30 to <40</td><td>DRV 450 mg</td><td>twice daily</td></tr>
<tr><td></td><td>RTV 60 mg</td><td>twice daily</td></tr>
<tr><td>≥ 40</td><td>DRV 600 mg</td><td>twice daily</td></tr>
<tr><td></td><td>RTV 100 mg</td><td>twice daily</td></tr>
</table>

Safety and efficacy has not been established in treatment experienced patients aged < 3 years who are < 10 kg or in treatment naïve patients < 12 years

<u>Once Daily Dosing</u>:
Considered for children ≥ 12 years and ≥ 40 kg who are treatment naïve or treatment experienced provided they do not have any DRV mutations
▪ DRV 800 mg + RTV 100 mg once daily
</td>
<td>Ritonavir available as:
▪ 100mg tablet
▪ 80 mg/mL oral solution (poor palatability with bad aftertaste)</td>
<td></td>
</tr>
<tr>
<td>Lopinavir/ Ritonavir (LPV/r) - Kaletra®

Product co-formulated with boosted dose Ritonavir (RTV)</td>
<td>For children > 6 months of age
<table>
<tr><th>Weight (kg)</th><th>TWICE daily dose (mg/kg)</th><th>Volume oral solution TWICE daily (mL)</th><th># of 100/25 tablets twice daily</th></tr>
<tr><td>7- <15</td><td>12 mg/kg</td><td colspan="2"></td></tr>
<tr><td>7-10</td><td rowspan="2"></td><td>1.25</td><td>-</td></tr>
<tr><td>>10-<15</td><td>1.75</td><td>-</td></tr>
<tr><td>10-40</td><td>10 mg/kg</td><td colspan="2"></td></tr>
<tr><td>15-20</td><td rowspan="5"></td><td>2.25</td><td>2</td></tr>
<tr><td>>20-25</td><td>2.75</td><td>2</td></tr>
<tr><td>>25-30</td><td>3.50</td><td>3</td></tr>
<tr><td>>30-35</td><td>4.00</td><td>3</td></tr>
<tr><td>>35-40</td><td>4.75</td><td>4 (or 2x200/ 50 mg tab)</td></tr>
</table>
*If given with concomitant efavirenz, nevirapine, nelfinavir or alprenavir must refer to drug</td>
<td>▪ Oral solution: 80 mg/20 mg LPV/r per mL (poor palatability; difficult to mask)

▪ Combination tablets: 100mg LPV/25mg RTV, 100mg LPV/25mg RTV</td>
<td>Give with food

Interacts with CYP P450 metabolized drugs

Oral solution contains 42.2% alcohol by volume and 15.3% propylene glycol by volume

<u>Do not administer oral solution</u> to neonates before a postnatal age of 42 weeks and a postnatal age of at least 14 days</td>
</tr>
</table>

<table>
<tr><td></td><td>product monograph for dosing recommendations</td><td></td><td></td></tr>
<tr><td colspan="4">Integrase Inhibitors</td></tr>
<tr><td>Raltegravir (RAL)</td><td>For children at least 12 years of age:
▪ One 400 mg tablet PO twice daily

For children 6 to < 12 years of age:
▪ ≥25 kg: one 400 mg film-coated tablet PO twice daily (may also use chewable tablets with weight based dose as specified in table below to maximum 300mg PO twice daily)
▪ <25 kg: use chewable tablets with weight based dose as specified in table below to maximum 300mg PO twice daily

For children 2 to < 6 years of age:
▪ use chewable tablets with weight based to maximum dose of 300 mg twice daily as specified below:

<table><tr><th>Body Weight (kg)</th><th>Dose (mg/dose)</th><th>Dose frequency</th></tr><tr><td>7 to < 10</td><td>50 mg chew tab</td><td>Twice daily</td></tr><tr><td>10 to <14</td><td>75 mg chew tab</td><td>Twice daily</td></tr><tr><td>14 to <20</td><td>100 mg chew tab</td><td>Twice daily</td></tr><tr><td>20 to <28</td><td>150 mg chew tab</td><td>Twice daily</td></tr><tr><td>28 to <40</td><td>200 mg chew tab</td><td>Twice daily</td></tr><tr><td>≥ 40</td><td>300 mg chew tab</td><td>Twice daily</td></tr></table>*weight based dosing for chewable tablet based on 6mg/kg/dose twice daily</td><td>▪ Chewable tablet: 25 mg, 100 mg (may be chewed or swallowed whole, 100 mg chew tab may be divided into equal halves)

▪ Film-coated tablet: 400mg – must be swallowed whole *for ≥6 years and ≥ 25 kg only</td><td>Give with or without food

Formulations are not bioequivalent – do not substitute chewable tablets for the 400 mg film-coated tablet

Chewable tablets contain phenylalanine – can be harmful in patients with phenylketonuria

Avoid co-administration of raltegravir within 2 hours of aluminum, magnesium hydroxide or calcium carbonate-containing antacids</td></tr>
<tr><td colspan="4">Multi-class combination formulations</td></tr>
<tr><td>Efavirenz-Tenofovir-Emtricitabine (EFV/TDF/FTC) - Atripla®</td><td>Should not be used in children < 40 kg where the EFV dose would be excessive

Weight ≥ 40 kg: 1 tablet PO</td><td>▪ Fixed-dose combination tablet: EFV 600 mg/ TDF 300 mg/ FTC 200mg</td><td>Give at bedtime

Take on an empty stomach to decrease side effects</td></tr>
</table>

	once daily		Interacts with CYP P450 metabolized drugs
Rilpivirine-Tenofovir-Emtricitabine (RPV/TDF/FTC) - Complera®	Not approved or recommended for use in children < 18 years Age ≥ 18 years: 1 tablet PO once daily	▪ Fixed-dose combination tablet: RPV 25 mg/ TDF 300 mg/ FTC 200mg	Take with a meal (500-600 kcal) Metabolized by CYP P450 3A Avoid concomitant administration with proton-pump inhibitors
Elvitegravir-Cobicistat-Tenofovir-Emtricitabine (EVG/COBI/FTC /TDF) - Stribild®	Not approved or recommended for use in children < 18 years. Age ≥ 18 years: 1 tablet PO once daily	▪ Fixed-dose combination tablet: EVG 150 mg/ COBI 150 mg/ FTC 200 mg/ TDF 300 mg	Take with food Caution concomitant nephrotoxic drugs Avoid co-administration of Stribild® within 2 hours of aluminum, magnesium hydroxide or calcium carbonate-containing antacids

PO = oral, IV = intravenous, kg = kilogram, mg = milligram