

IX: CARE OF THE CHILD WITH HIV INFECTION, INCLUDING CONSIDERATIONS OF ANTIRETROVIRAL THERAPY

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IX. CARE OF THE CHILD WITH HIV INFECTION, INCLUDING CONSIDERATIONS OF ANTIRETROVIRAL THERAPY

BACKGROUND

HIV/AIDS is the first or second leading cause of death in Caribbean children age one to four years. In the Caribbean, HIV is transmitted to infants *in utero*, during delivery, via breastfeeding, and due to sexual abuse.

The Caribbean is extremely diverse with regard to expertise, healthcare facilities, laboratory diagnostic capabilities, and treatment options for managing infants and children with HIV/AIDS. Recognising this diversity, the recommendations in this chapter are drawn primarily from the World Health Organisation (WHO), the U.S. National Institutes of Health (NIH), and the U.S. Centers for Disease Control and Prevention (CDC). Wherever possible, HIV-infected infants and children should be managed by clinicians experienced in the use and monitoring of antiretroviral therapy (ART) as well as in the identification and treatment of opportunistic infections (OIs) in HIV-infected children.

With low-cost antiretroviral drugs (ARVs) now more available in the region, expertise in the administration of Highly Active Antiretroviral Therapy (HAART) for Caribbean children is critical. Numerous studies, including data from the Caribbean,¹ have established the remarkable efficacy of HAART in reducing HIV-associated morbidity and mortality in paediatric populations. It should be remembered, however, that these medications are an essential but incomplete part of the healthcare equation for the HIV patient. The commitment to treat is a life-long contract, encompassing the development of a support system for the patient and family.

DIAGNOSIS AND CLASSIFICATION OF PAEDIATRIC HIV/AIDS

WHO and CDC HIV/AIDS classification systems for infants and children age thirteen or younger are presented in *Appendix C*. WHO recognises that this staging system can overlap with several other conditions in children seen in resource-poor settings, and this system is currently under revision.

Alternatively, CDC's revised criteria may be used, which offers more specific clinical diagnostic categories of A, B, and C for mild, moderate, and severe disease respectively and immunological criteria of classes 1, 2, and 3 for mild, moderate, and severe immunosuppression respectively.

OI PROPHYLAXIS AND IMMUNISATIONS

The management of the HIV-exposed infant, including considerations of prophylaxis against *Pneumocystis jiroveci* pneumonia (PCP), are summarised in *Chapter VIII: Care of Children Born to HIV-Infected Mothers*. The diagnosis and management of OIs in HIV-infected children are detailed in *Chapter X: Diagnosis and Treatment of Opportunistic Infections (OIs) among HIV-Exposed and -Infected Children*, while paediatric OI prophylaxis recommendations are summarised in *Chapter VI: Recommendations for Adult and Paediatric Opportunistic Infections (OIs) Prophylaxis*. Immunisation recommendations are detailed in *Chapter VI, Table 4*.

Tuberculosis (TB)

TB deserves special mention for reasons related to epidemiology, diagnosis, and treatment. Alarming increases in active TB in Caribbean children have been recently documented in Jamaica and Haiti. HIV co-infection among paediatric TB cases has increased dramatically as well, with rates of 50% in some

prospective studies.² These children usually have close household exposures and/or contact to family members with active (and often undiagnosed) TB.

Paediatric TB-HIV co-infection presents several diagnostic challenges. TB and HIV infection have the same features of chronic cough, recurrent fever, growth failure, lymphadenopathy, and abnormal chest radiographs. Children with HIV/AIDS are often anergic and may not respond to the Mantoux skin test.

Experience in the management of Jamaican children with TB-HIV co-infection has suggested that those who were treated with TB medications alone typically improved initially, but subsequently deteriorated or died, whereas those treated with anti-TB medications *and* HAART usually improved. Hence, treatment with both HAART and anti-TB drugs generally leads to improved survival and the best long-term outcomes in children with TB-HIV co-infection. However, the timing of HAART initiation as well as the selection of the initial HAART regimen must be considered carefully and should be performed in consultation with an expert in the management of both diseases.

INITIATION OF HAART IN PAEDIATRIC PATIENTS: GENERAL CONSIDERATIONS

HAART, defined as the combination of three or more antiretroviral agents taken concurrently to suppress HIV replication, represents the current standard of care of antiretroviral therapy for children infected with HIV. This strategy evolved from the recognition that treatment of chronic HIV infection with only one or two ARV agents typically results in rapid treatment failure and the development of ARV resistance, compromising future therapeutic options.

These recommendations provide general guidance rather than absolute recommendations for the individual patient. As is true for adult antiretroviral therapy, many factors must be considered in deciding whether to initiate HAART including:

- the potential benefits and risks of therapy;
- the ability of the caregiver and child to adhere to administration of the therapeutic regimen (discussed in more detail below); and
- the risk of disease progression as suggested by the CD4+ T cell count and HIV viral load (if these tests are available).

HIV infection generally progresses more rapidly in children than in adults. Without treatment, about 50% of adults develop AIDS ten years post-infection, whereas approximately 50% of children will develop AIDS three years post-infection, and 25% by twelve months without effective HAART. Infants are at particular risk for rapid disease progression and are especially vulnerable to central nervous system (CNS) complications. It is impossible to predict which infants will progress rapidly, hence many experts recommend that all infants found to be HIV-infected before age one year be treated with HAART.

The laboratory diagnosis of HIV infection in infants age eighteen months or younger is difficult due to the persistence of maternal antibodies against HIV. Virologic tests are therefore required to make the definitive diagnosis of HIV infection in this age group, as reviewed in *Chapter VIII*.

The penetration of antiretroviral medications (ARVs) into human breastmilk in lactating women has not been quantified for most of these agents. If an ARV is secreted into breastmilk, the quantity and concentration may not be sufficient to achieve therapeutic levels in the infants. Therefore, ARVs should be given in standard doses to infants who require it regardless of whether the mother is receiving antiretroviral therapy.

Recommendations for initiation of HAART in Caribbean HIV-infected children are derived from WHO guidelines for resource-constrained settings and from the NIH and CDC for more resource-rich regions.

RECOMMENDATIONS FOR INITIATION OF HAART IN RESOURCE-CONSTRAINED SETTINGS: WHO GUIDELINES

WHO recommendations for initiation of HAART depend on the child's age and on the availability of virologic and CD4+ T cell testing. Where CD4+ T cell assays are available, the use of the CD4+ T cell percentage, rather than the absolute CD4+ T cell count, is recommended because the CD4+ T cell percentage varies less with age. The total lymphocyte count (TLC) also correlates with the risk of mortality in symptomatic HIV-infected children, and may be used instead of the CD4+ T cell count in these patients where CD4+ T cell testing is unavailable.

Despite cost constraints, the WHO recommends the development of tests applicable to resource-limited settings that would allow early diagnosis of HIV infection in infants. The availability of such tests is critical to the development of improved recommendations for therapy initiation in infants age eighteen months or younger.

The WHO guidelines for initiating HAART in resource-constrained settings are summarised in *Table 1a* and *Table 1b*.

Table 1: WHO Guidelines for Initiation of HAART in Resource-Limited Settings³

Table 1a: Recommendations for Initiating HAART in Infants and Children if CD4+ T Cell Count Testing Is Available

AGE	HIV DIAGNOSTIC TESTING	TREATMENT RECOMMENDATION
<18 months	HIV virologic testing not available but infant is HIV antibody-seropositive**	WHO Paediatric Stages II and III disease and CD4+ T cell count <20% ^a
	Positive HIV virologic test ^b	WHO Paediatric Stage III (e.g. AIDS) irrespective of CD4+ T cell percentage WHO Paediatric Stage II disease (with consideration of using CD4+ T cell count of <20% to assist in decision-making) ^{a,c} WHO Paediatric Stage I disease (e.g. asymptomatic) and CD4+ T cell count of <20% ^{a,d}
≥18 months	HIV antibody-seropositive	WHO Paediatric Stage III disease, irrespective of CD4+ T cell percentage WHO Paediatric Stage II disease (with consideration for using CD4+ T cell count of <15% to assist in decision-making) WHO Paediatric Stage I disease and CD4+ T cell count of <15%

Table 1b: Recommendations for Initiating HAART in Infants and Children if CD4+ T Cell Count Testing Is Not Available

AGE	HIV DIAGNOSTIC TESTING	TREATMENT RECOMMENDATION
<18 months	HIV virologic testing not available but infant is HIV antibody-seropositive	Treatment not recommended ^{d,e}
	Positive HIV virologic test ^b	WHO Paediatric Stage III, irrespective of TLC WHO Paediatric Stage II disease (with consideration for using the TLC of <2,500/mm ³ to assist in decision-making) ^f
≥18 months	HIV antibody-seropositive	WHO Paediatric Stage III, irrespective of TLC* WHO Paediatric Stage II disease (with consideration for using the TLC of <1,500/mm ³ to assist in decision-making) ^f

**HIV serologic testing must be repeated at age eighteen months to obtain definitive diagnosis of HIV infection.

^aA CD4+ T cell count of <20% corresponds to an absolute CD4+ T cell count of approximately <1,000/mm³ for children age twelve months or younger and <750/mm³ for children age twelve to eighteen months; a CD4+ T cell count of <15% corresponds to <500/mm³ for children age one to five years and to <200/mm³ for children age six years or younger.

^bHIV DNA PCR or HIV RNA amplification assays or immune complex disassociated p24 antigen assays.

^cA CD4+ T cell percentage is advisable to assist with determining the need for immediate therapy.

^dIf a child is asymptomatic and treatment is being initiated on a basis of CD4+ T cell count criteria, consideration should be given to performing a confirmatory CD4+ T cell assay if resources permit.

^eMany of the clinical symptoms in WHO Paediatric Stage II and III disease classifications are not specific for HIV infection and significantly overlap with those seen in children without HIV infection in resource-limited settings; thus, in the absence of virological testing and CD4+ T cell count availability, symptomatic

seropositive infants age eighteen months or younger should only be considered for HAART in exceptional circumstances (e.g. a child with a classic AIDS-defining condition such as PCP or cryptococcal meningitis). If ARVs are given to a symptomatic HIV-positive infant in the absence of a definitive virological diagnosis, HIV antibody testing should be repeated at age eighteen months to confirm infection status; HAART should only be continued in infants with confirmed HIV infection.

^f A total lymphocyte count of $<2,500/\text{mm}^3$ for children age eighteen months or younger or $<1,500/\text{mm}^3$ for children age eighteen months or older can be substituted for CD4+ T cell percentage when the latter is unavailable and HIV-related symptoms exist. Its utility in asymptomatic children is unknown. In the absence of CD4+ T cell testing, therefore, asymptomatic HIV-infected children (WHO Paediatric Stage I) should not be treated because no other reliable marker is currently available in severely resource-constrained settings.

RECOMMENDATIONS FOR INITIATION OF HAART IN RESOURCE-FULL SETTINGS: NIH AND CDC GUIDELINES

It is recommended that Caribbean settings with more resources use the NPHRC/HRSA/NIH guidelines for deciding when to commence HAART in infants and children (*Tables 2 and 3*).⁴ It should be noted that many clinicians would recommend treatment of all HIV-infected children age one year or younger, regardless of clinical, immunological, or virologic status. Infancy represents a period when there is usually a very high viral load with a high risk for rapid progression of HIV disease and the potential to develop irreversible brain injury as a result of HIV encephalopathy.

Table 2: Indications for Initiation of HAART in HIV-Infected Children Age One Year or Younger in Resource-Rich Settings

CLINICAL CATEGORY		CD4+ CELL PERCENTAGE	PLASMA HIV RNA COPY NUMBER*	RECOMMENDATION
Symptomatic (Clinical category A, B, or C)	OR	<25% (Immune category 2 or 3)	Any value	Treat
Asymptomatic (Clinical category N)	AND	≥25% (Immune category 1)	Any value	Consider Treatment**

* Plasma HIV RNA levels are higher in HIV-infected infants than in older infected children and adults, and may be difficult to interpret in infants age twelve months or younger because overall HIV RNA levels are high and there is overlap in HIV RNA levels between infants who have and those who do not have rapid disease progression.

** Because HIV infection progresses more rapidly in infants than in older children or adults, some experts would treat all HIV-infected infants age six months or younger or age twelve months or younger regardless of clinical, immunologic, or virologic parameters.

Adapted from: NPHRC/HRSA/NIH. *Guidelines for the use of antiretroviral agents in pediatric HIV infection.* 30 November 2004. Accessed 2004. Available at: http://aidsinfo.nih.gov/guidelines/default_db2.asp?id=51.

Table 3: Indications for Initiation of HAART in HIV-Infected Children Age One Year or Older in Resource-Rich Settings

CLINICAL CATEGORY		CD4+ CELL PERCENTAGE		PLASMA HIV RNA COPY NUMBER	RECOMMENDATION
AIDS (Clinical category C)	OR	<15% (Immune category 3)		Any value	Treat
Mild-Moderate Symptoms (Clinical category A or B)	OR	15-25%* (Immune Category 2)	OR	≥100,000 copies/mL**	Consider Treatment
Asymptomatic (Clinical category N)	AND	>25% (Immune Category 1)	AND	<100,000 copies/mL**	Many experts would defer therapy and closely monitor clinical, immune and viral parameters

*Many experts would initiate therapy if CD4+ T cell percentage is between 15% to 20% and defer therapy with increased monitoring frequency in children with CD4+ T cell percentage of 21% to 25%.

**There is controversy among paediatric HIV experts regarding the plasma HIV RNA threshold warranting consideration of therapy in children in the absence of clinical or immune abnormalities; some experts would consider initiation of therapy in asymptomatic children if plasma HIV RNA levels are between 50,000 to 100,000 copies/mL.

Adapted from: NPHRC/HRSA/NIH. Guidelines for the use of antiretroviral agents in pediatric HIV infection. 30 November 2004. Accessed 2004. Available at: http://aidsinfo.nih.gov/guidelines/default_db2.asp?id=51.

PRACTICAL CONSIDERATIONS FOR THE CARIBBEAN

In practice, all confirmed HIV-infected children in the Caribbean should be treated, in decreasing order of importance, for:

- TB;
- Severe failure to thrive;
- Encephalopathy;
- Meningitis or septicaemia;
- Hospitalisation for HIV-related illnesses;
- CDC Category C, then B, disease; and
- Any known HIV-infected child who is age one year or younger.

Additionally, efforts must be made to ensure ongoing adherence, access to medications, and care for those children who merit HAART. HAART should generally be delayed if the patient is stable and there are unresolved issues of non-adherence.

ADHERENCE

The success or failure of antiretroviral therapy for children--as well as for adults--depends primarily on the ability of the patient to take ARVs as prescribed. For this reason, intensive efforts should be made prior to and following initiation of antiretroviral therapy to promote optimal adherence. These interventions must necessarily involve the family and/or caregiver(s) of the child being treated. Practical strategies to promote adherence include:

- Carefully assessing and preparing the family for adherence to medications and care, including nursing, social, behavioural, and psychological assessments.
- Establishing trust and identification of mutually acceptable goals for care.
- Gathering information regarding the obtaining, storing, and administering of the child's medications.
- Determining who is responsible for administering medications and exactly how this is performed.
- Providing intensive family education and medication training before initiating treatment.
- Educating the family about the relationship between partial adherence and resistance.
- Educating the family that at the age of approximately three years, children can be successfully trained to take pills without adverse experiences or behavioural problems.
 - Training is best achieved by a neutral and non-authoritative individual who is not a family member.
 - Useful techniques for training a child to take pills include encouraging him/her to relax, using increasing sizes of placebo pills, and encouraging swallowing with water or other liquids.
- Facilitating encouragement with minimal extrinsic rewards.
- Not allowing the child to refuse medications once the child begins to take ARVs.
- Disallowing other activities until the ARVs are taken.
- Monitoring adherence at each visit, or between visits by phone.
- Providing ongoing support and encouragement.
- Considering a period of hospitalisation for virologic failure to assess adherence and to reinforce that medication adherence is fundamental to successful HAART.

RECOMMENDED INITIAL PAEDIATRIC HAART REGIMENS

The preferred paediatric initial regimens are summarised in *Table 4*. Three or more ARVs (generally two NRTIs--the *NRTI backbone*--combined with either an NNRTI or a PI) should always be used in conjunction to maximise the probability of sustained virologic suppression and to minimise the possibility of the development of resistance. The use of zidovudine (AZT)/lamivudine (3TC)/abacavir (ABC) as a first-line therapy is now considered a secondary alternative due to recent data from a clinical trial in HIV-infected adults (ACTG 5095a) demonstrating a significantly higher failure rate in individuals receiving this regimen than in individuals receiving similar efavirenz (EFV)-based regimens.

Preferred dual NRTI backbones include AZT plus 3TC; AZT plus didanosine (ddI); or stavudine (d4T) plus 3TC. AZT penetrates the blood brain barrier and is therefore ideally suited for infancy given the risk of HIV encephalopathy and developmental delay in this age group. d4T can be substituted for AZT if the child is anaemic or experiences AZT-related toxicity. 3TC is generally preferred over ddI for pairing with AZT and d4T because 3TC is highly potent, generally well-tolerated, and available in simple dosing formulations. EFV is not recommended in children age three years or younger or weighing less than twenty-five pounds due to the lack of dosing information and an appropriate formulation.

HAART regimens must be based on sound virologic and pharmacologic principles but must also be acceptable to the individual patient. Thus, the design of the HAART regimen is influenced by considerations of drug potency, side effect profiles, laboratory monitoring requirements, potential for maintenance of future treatment options, anticipated patient adherence, co-existent conditions, concomitant medications, availability, and cost. The potential for ARV resistance in infants infected despite ARV PMTCT prophylaxis should also be considered in the design of the HAART regimen; this issue is discussed in more detail in the section that immediately follows.

ARVs can be given to children in liquid formulations or in pills. Drug doses must be continually adjusted as the child grows to avoid under-dosing, which could lead to the development of ARV resistance. Regimens should consider the timing and interval between doses to maximise adherence. Combination formulations of ARVs are not readily available for infants and children. Nevertheless, until appropriate paediatric formulations can be made more widely available, splitting adult-dose solid formulation ARVs may be the only way a severely ill child can receive appropriate ART when no alternatives are available.

Currently available paediatric dosages and formulations of ARVs are presented in *Appendix B*, as well as significant adverse effects and toxicities associated with these ARVs.

Risk of ARV resistance in Infants Who Become Infected Despite PMTCT Prophylaxis

Infants who become infected with HIV despite antiretroviral PMTCT prophylaxis may be infected with drug-resistant virus. This is most likely to occur with PMTCT regimens using ARVs for which a single point mutation can confer drug resistance, such as NVP or 3TC; resistance is less likely to develop to ARVs for which prolonged exposure and multiple mutations are associated with resistance, such as AZT.

Hence, infants who receive SD NVP (with or without other ARVs) and become infected with HIV despite this intervention are at risk for harbouring a strain of HIV that is resistant to NVP (and by extension, to other NNRTIs, since cross-resistance in the NNRTI class is very common). This phenomenon has been documented in several clinical trials, with a range of 8 to 52% of NVP-exposed infants demonstrating NVP resistance when tested within several weeks of birth. The risk appears to be elevated in infants whose mothers also received SD NVP during labour. In theory, the development of NVP resistance in this fashion could compromise the infant's response to future NNRTI-based HAART regimens; clinical trials are underway that will hopefully answer this important question. Until more data become available, clinicians managing HIV-infected infants who were exposed to SD NVP may consider favouring PI-based HAART regimens over NNRTI-based regimens. However, if a PI-based regimen is not readily

available or is impractical for other reasons, NNRTI-based HAART can and should be used for these infants.

Variable patterns of resistance to other ARVs such as AZT and 3TC in infants exposed to these agents have also been documented. In PACTG 076, where mothers received AZT starting at 14-34 weeks gestation and infants received 6 weeks of AZT, no AZT resistance was observed in infected infants; however, in PACTG 185, where the PACTG 076 AZT regimen was given but the women were sicker at entry, 30% of infected infants had AZT resistance. In a Thai study of short-course AZT, 20% of infants infected despite prophylaxis had AZT-resistant virus. In a study in France in which 3TC was added to AZT after 32 weeks gestation and the infants received 6 weeks of AZT/3TC, 3TC resistance was observed in 2 of 5 infected infants (40%); AZT resistance was seen in 2/5 infected infants as well. In the SAINT study, where AZT/3TC was administered during labour and post-partum, no AZT or 3TC resistance was observed in infected infants. As is the case with NVP, the clinical implications remain unclear; hence, exposure to PMTCT regimens that include AZT or 3TC should not preclude the inclusion of these agents in future HAART regimens for HIV-infected infants.

Table 4: Recommended Initial HAART Regimens for HIV-Infected Children⁵

Non-Nucleoside Reverse Transcriptase Inhibitor (NNRTI)-Based Regimens	
Strongly Recommended:	Age >3 years: 2 NRTIs ^a + EFV ^b (with or without nelfinavir (NFV)) Age <3 years or who cannot swallow capsules: 2 NRTIs ^a + NVP ^b
Alternative Recommendation:	2 NRTIs ^a + NVP ^b (age >3 years)
Protease Inhibitor (PI)-Based Regimens	
Strongly Recommended:	2 NRTIs ^a + LPV (lopinavir)/r (Kaletra [®]) or NFV or ritonavir (RTV)
Alternative Recommendation:	2 NRTIs ^a + indinavir (IDV) or amprenavir (APV) ^c
Triple Nucleoside Reverse Transcriptase Inhibitor (NRTI) Regimens	
Strongly Recommended:	None
Alternative Recommendation:	AZT + 3TC + ABC
Regimens Not Recommended	
	Monotherapy ^d
	Certain 2 NRTI ^a combinations
	2 NRTIs ^a + saquinavir (SQV) as sole PI ^d
Insufficient Data to Recommend	
	2 NRTIs ^a + delavirdine (DLV)
	Dual PIs with the exception of LPV/r ^e
	1 NRTI + 1 NNRTI + 1 PI ^f
	Regimens that contain tenofovir (TDF), atazanavir (ATV), emtricitabine (FTC), fos-amprenavir, or enfuvirtide

^a Dual NRTI combination recommendations:

- Strongly Recommended: AZT + ddi + 3TC; or d4T + 3TC
- Alternative Choices: ABC + AZT or 3TC; or ddi + 3TC
- Use in Special Circumstances: d4T + ddi; or zalcitabine (ddC) + AZT
- Insufficient Data: TDF- or FTC-containing regimens
- Not Recommended: ddC + ddi, d4T, or 3TC; or AZT + d4T

^b EFV is currently available only in capsule form, although a liquid formulation is currently under study to determine appropriate dosage in HIV-infected children age three years or younger; NVP would be the preferred NNRTI for children age three years or younger or who require a liquid formulation.

^c APV should not be administered to children age four years or younger due to the propylene glycol and vitamin E content of the oral liquid preparation and lack of pharmacokinetic data in this age group.

^d Except for AZT chemoprophylaxis administered to HIV-exposed infants during the first six weeks of life to prevent perinatal HIV transmission; if an infant is confirmed as HIV-infected while receiving AZT prophylaxis, therapy should either be discontinued or changed to a combination ARV drug regimen.

^e With the exception of LPV/r, data on the pharmacokinetics and safety of dual PI combinations (e.g. low-dose RTV pharmacologic boosting of SQV, IDV, APV, or NFV) are limited, use of dual PIs as a component of initial therapy is not recommended, although such regimens may have utility as secondary treatment regimens for children who have failed initial therapy. SQV soft and hard gel capsules require low-dose RTV-boosting to achieve adequate levels in children, but pharmacokinetic data on appropriate dosing are not yet available.

^f With the exception of EFV + NFV + one or two NRTIs, which has been studied in HIV-infected children and shown to have virologic and immunologic efficacy in a clinical trial.

SPECIAL CONSIDERATIONS FOR PATIENTS WITH TB

Special considerations around antiretroviral therapy must be made for the child co-infected with HIV and TB:

- ***Selection of the Initial HAART Regimen:*** NVP is generally avoided due to significant interactions with rifamycin. If EFV- or PI-based regimens are not an option, administration of the triple-NRTI regimen AZT plus 3TC plus ABC should be considered.
- ***Timing of HAART Initiation:*** The optimal time to initiate HAART in patients with TB is unclear and should be considered on a case-by-case basis. Clinical experience in Jamaica suggests that survival is improved in co-infected children who receive both HAART and TB treatment. However, it may be advisable to delay the initiation of HAART for two to eight weeks following the initiation of anti-TB medications in order to minimise pill burden, drug-drug interactions, overlapping toxicities, and the risk of immune reconstitution syndrome (IRS).^{*} Hence, deferral of HAART initiation until after the induction phase of TB therapy may be advisable for those children without clinical or immunological evidence of advanced HIV disease.

CLINICAL MONITORING AND FOLLOW-UP

The goals of therapy are to achieve and to maintain an undetectable HIV viral load. This prevents disease progression, optimises recovery of the immune system, and prevents antiretroviral drug resistance. An effective HAART regimen should generally result in an undetectable (e.g. less than 50 copies/mL) HIV viral load within six months of therapy initiation. Suboptimal adherence is the most common reason for failure of the initial HAART regimen. Adherence should therefore be monitored closely following therapy initiation using pill counts, pharmacy prescription refill logs, and patient/caregiver self-reports. Failure to achieve an undetectable viral load following initiation of HAART should prompt evaluation of adherence and potential drug resistance. Common reasons for suboptimal adherence include drug side effects, dosing difficulties, and inconvenience of administration.

If an undetectable HIV viral load is achieved, a significant rise in the CD4+ T cell count generally occurs, signifying partial reconstitution of the immune system. However, the degree of rise of the CD4+ T cell count can be quite variable, and some patients may not experience a significant rise in the CD4+ T cell count despite a dramatic reduction in viraemia. The optimal management of patients with this *discordant response* remains unclear, but should be based in part on consideration of clinical response to therapy. Consultation with an expert in paediatric HIV management is also recommended.

Clinical markers that suggest a positive response to HAART include:

- reduced hospitalisations;
- increased appetite, weight, and height (in children with failure to thrive);
- improved brain growth, neurodevelopment, affect, and head circumference (in those with developmental delay and/or encephalopathy); and
- reduced morbidity with reduced OIs and minor co-morbid illnesses (e.g. papular prurigo, otitis media, oral thrush, upper respiratory tract infections).

TREATMENT TOXICITY

While adverse effects from HAART are common, they can usually be managed symptomatically while continuing the HAART regimen without interruption, as most adverse effects associated with ARVs resolve within one to three months of therapy initiation. If the adverse effect is severe enough to require modification of the regimen, substitution of the offending drug with another ARV is a reasonable option

^{*}See the introduction to *Chapter V: Recommendations for the Treatment of Opportunistic Infections among Adults and Adolescents* for a review of the pathophysiology and clinical presentation of IRS.

if it can be reasonably deduced which agent is responsible for the side effect in question. *Table 5* presents options for drug substitution in the event of selected common adverse reactions. Consultation with an expert HIV clinician is strongly recommended when a regimen change is necessary.

Table 5: Common Adverse Drug Reactions Associated with First-Line HAART Regimens and Recommended Drug Substitutions⁶

REGIMEN	TOXICITY	DRUG SUBSTITUTION
d4T/3TC/NVP	<ul style="list-style-type: none"> d4T-related neuropathy or pancreatitis d4T-related lipoatrophy NVP-related severe hepatotoxicity NVP-related severe rash (but not life-threatening) NVP-related life-threatening rash (e.g. Stevens-Johnson syndrome) 	Switch d4T → AZT Switch d4T → ABC [†] Switch NVP → EFV [‡] Switch NVP → EFV Switch NVP → PI [§]
AZT/3TC/NVP	<ul style="list-style-type: none"> AZT-related persistent GI intolerance or severe haematological toxicity NVP-related severe hepatotoxicity NVP-related severe rash (but not life-threatening) NVP-related life-threatening rash (e.g. Stevens-Johnson syndrome) 	Switch AZT → d4T Switch NVP → EFV Switch NVP → EFV Switch NVP → PI
d4T/3TC/EFV	<ul style="list-style-type: none"> d4T-related neuropathy or pancreatitis d4T-related lipoatrophy EFV-related persistent CNS toxicity 	Switch d4T → AZT Switch d4T → ABC Switch EFV → NVP
AZT/3TC/EFV	<ul style="list-style-type: none"> AZT-related persistent GI intolerance or severe haematological toxicity EFV-related persistent CNS toxicity 	Switch AZT → d4T Switch EFV → NVP

Occasionally, severe HAART-related toxicity requires discontinuation of all ARV agents. In such circumstances, it is best to discontinue all medications simultaneously, because continuation of therapy with only one or two ARV agents is associated with the development of drug resistance.** HAART should be withheld until the patient recovers, at which time re-initiation of therapy with a different regimen can be considered in consultation with an HIV expert.

[†]Switching off d4T appears to reduce, and in some cases reverse, lipoatrophy, though very slowly. TDF and ABC represent the best alternatives to d4T in this setting, but their availability in the Caribbean is limited, and TDF cannot be recommended for paediatric use given insufficient data. ddI and AZT are reasonable alternatives where ABC is not available.

[‡]Except in pregnancy. If the child is a teenager of child-bearing age who is pregnant or at risk for becoming pregnant, substitute a PI (preferred) or ABC.

[§]Recommended PIs include LPV/r or NFV or SQV/r.

**If the HAART regimen being discontinued contains an NNRTI (e.g. NVP or EFV), some expert clinicians would recommend discontinuing the NNRTI three to seven days prior to discontinuing the NRTIs, owing to the prolonged plasma half-life of NNRTIs.

TREATMENT FAILURE

Treatment failure refers to the absence of a sustained favourable response to HAART. Treatment failure can be suspected on the basis of clinical grounds, but confirmation of failure with laboratory testing is strongly recommended before changing a patient's HAART regimen. Consultation with an expert HIV clinician is also highly recommended if treatment failure is suspected on the basis of clinical, immunologic, or virologic criteria. Efforts should be made to confirm suspected treatment failure as rapidly as possible to prevent HIV disease progression and the development of further resistance to ARV agents. Laboratory testing can be useful both to establish treatment failure and in guiding second-line treatment options.

In the event of treatment failure, re-assessment of adherence is indicated. After adherence issues have been adequately addressed, a change in the HAART regimen to second-line therapy is usually warranted, as detailed later in this section.

Treatment Failure: Virologic Definition

With successful initial HAART, the HIV viral load is expected to decline by at least tenfold (one \log_{10}) every two to eight weeks, and should be below the limit of detection of most viral load assays within approximately six months of HAART initiation. Treatment failure can be defined by the absence of such a decline in HIV viral load following initiation of therapy (*failure to suppress*), or by virologic suppression to below the lower limit of detection followed by a subsequent sustained rise in HIV viraemia (*virologic breakthrough*). These concepts are represented graphically in *Chapter IV, Figures 3 and 4*. If HIV viral load testing confirms treatment failure, consideration of second-line therapy in consultation with an HIV expert is recommended. Efforts should be made to change the HAART regimen as soon as possible to discourage the development of drug resistance and to preserve effective treatment options. Where viral load testing is not available, treatment failure can be made on the basis of immunologic or clinical criteria, as described below.

Treatment Failure: Immunologic Definition

Because of age-related declines in absolute CD4+ T cell counts until age six years when near-adult levels are reached, it is difficult to use such counts for assessing therapy failure in younger children. However, for children age six years or older, similar CD4+ T cell count criteria to those used for adults are appropriate. CD4+ T cell percentage varies less with age and is therefore more appropriate than the absolute CD4+ T cell count for gauging treatment response in younger children. Where resources permit, confirmatory repeat CD4+ T cell testing or viral load testing is warranted for the asymptomatic child suspected of failure based on immunologic criteria alone. No data exist regarding the use of the total lymphocyte count (TLC) for the evaluation of response to HAART in children.

U.S. Pediatric Guidelines⁷ suggest the following criteria for immunologic failure:

- Change in CDC immunologic classification (see *Appendix C* for immunologic classification schemes);^{***} or
- For children with CD4+ T cell percentages of <15% (e.g. those in immune category 3), a persistent decline of $\geq 5\%$ in CD4+ T cell percentage (e.g. from 15% to 10%); or
- A rapid and substantial decrease in absolute CD4+ T cell count (e.g. >30% decline in less than six months).

^{***}Minimal changes in CD4+ T cell percentile that may result in change in immunologic category (e.g. from 26% to 24%, or 16% to 14%) may not be as concerning as a rapid substantial change in CD4+ T cell percentile within the same immunologic category (e.g. a drop from 35% to 25%).

WHO criteria⁸ for treatment failure in children include:

- Return of CD4+ T cell percentage (or for children age six years or older, of absolute CD4+ T cell count) to pre-therapy baseline or below, in absence of other concurrent infection explaining transient CD4+ T cell decrease; or
- >50% fall from peak level on therapy of CD4+ T cell percentage (or for children age six years or older, of absolute CD4+ T cell count) in absence of other concurrent infection explaining transient CD4+ T cell decrease.

Treatment Failure: Clinical Definition

Treatment failure should be suspected if progression of HIV disease continues following HAART initiation or if no clinical improvement occurs in three months following therapy initiation. Clinicians must be careful to distinguish suspected HIV disease progression from IRS, which can also manifest with fevers, night sweats, and fatigue, but does not signify treatment failure. IRS typically resolves within a couple of months following initiation of HAART, whereas a new OI generally will not. Further discussion of IRS can be found in the introduction to *Chapter V: Recommendations for the Treatment of Opportunistic Infections among Adults and Adolescents*.

In children, important clinical signs of treatment failure include:

- lack of growth, or falling off of growth in children with an initial growth response;
- loss of neurodevelopmental milestones or development of encephalopathy;
- occurrence of new OIs or of a malignancy signifying clinical disease progression;^{†††} and
- recurrence of minor and major OIs that may be refractory to therapy, e.g. oral candidiasis.

Management of Suspected Treatment Failure

It should not be concluded on the basis of clinical criteria alone that a HAART regimen is failing until the child in question has had a reasonable treatment trial (e.g. receiving the regimen for at least twenty-four weeks). The HAART regimen should not be changed unless ongoing poor adherence has been ruled out for failure. Laboratory testing at six months, especially viral load testing, is strongly recommended if treatment failure is still suspected six months following the initiation of HAART. The viral load results should be confirmed, if possible, to ensure that the suggested change is needed. Laboratory results should be reviewed with an expert HIV clinician to guide management decisions. If treatment failure is confirmed, a change in HAART to a second-line regimen is generally recommended, although if a regimen has brought the viral load to low or nearly undetectable levels, intensification of the current regimen with the addition of another drug may be a reasonable alternative strategy.

Where reasonable options for second-line HAART regimens are lacking, it may be more advantageous to continue the initial HAART regimen despite a suboptimal response rather than change regimens. However, it should be recognised that this approach risks the ongoing development of ARV drug resistance, which can further compromise future treatment options.

SECOND-LINE AND SALVAGE ANTIRETROVIRAL THERAPY

Treatment failure of the initial HAART regimen is a common, though not inevitable, event. When initial treatment fails, a second-line regimen is generally implemented. *Salvage therapy* refers to treatment regimens designed for patients who have failed two or more ARV regimens. In general, each successive HAART regimen is less likely than the previous regimen to achieve durable virologic and immunologic

^{†††}This must be distinguished from IRS, which can occur in the first three months following HAART initiation and does not signify treatment failure.

success. Hence, treatment regimens must be selected carefully to maximise a patient's likelihood of a robust and durable response to HAART.

HIV RESISTANCE TO ARV MEDICATIONS

Treatment failure often (though not always) occurs because a patient's strain of HIV has developed resistance to one or more of his or her ARVs. The development of resistance by HIV is similar to the way in which bacteria or mycobacteria (e.g. TB) develop resistance to antibiotics: insufficiently potent drug therapy selects for mutant strains that are resistant to the medications administered to the patient. These mutant strains then replace the wild-type strain due to their selective replication advantage in the face of drug pressure, leading to treatment failure. Resistance to ARVs most commonly develops in the setting of suboptimal adherence, but can occur even in patients who maintain very high levels of adherence to their medications. For example, a patient with poorly-controlled diarrhoea may not fully absorb his or her medications, leading to subtherapeutic drug levels in the blood, which could lead to the development of resistance.

Cross-resistance between ARV drugs within drug classes is common; for example, a strain of HIV that is resistant to NVP is very likely to be highly resistant to EFV as well, and *vice versa*. Considerations of potential cross-resistance must therefore be incorporated into the design of second-line and salvage treatment regimens.

Laboratory assays have been developed to estimate the patterns of resistance that have developed in a given patient's strain of HIV. Though imperfect, these assays have demonstrated clinical efficacy in aiding the design of second-line treatment regimens following treatment failure. Unfortunately, these assays are very expensive and not widely available in the Caribbean. However, where available, a resistance assay can provide valuable information for patients experiencing treatment failure.

Even in the absence of resistance testing, knowledge of the patterns of resistance and cross-resistance that commonly develop in patients failing specific regimens allows for reasonably accurate empiric decision-making in designing a second-line regimen. Empirically designed algorithms have been incorporated into the design of second-line treatment regimens (see *Table 6*).

A more detailed discussion of ARV resistance and resistance assays can be found in *Appendix F* of *Chapter IV*.

SECOND-LINE HAART REGIMENS

Second-line HAART regimens are indicated for patients who are forced to discontinue their initial treatment regimen as a consequence of treatment failure or severe toxicity. Consultation with an expert HIV clinician is highly recommended when designing a second-line regimen. If the initial regimen was discontinued due to toxicity without evidence of treatment failure, then the second-line regimen should involve substitution of the drug most likely to be responsible for the toxicity, as outlined in *Table 5*. For example, if a child develops a severe skin rash after starting an initial regimen of d4T plus 3TC plus NVP, a second-line regimen can be constructed using the same nucleoside backbone but with a different third agent, because it can be reasonably assumed that the NVP was responsible for the skin reaction.⁹

If the initial HAART regimen was discontinued due to treatment failure, however, it is likely that drug resistance to one or more ARV agents in the initial regimen has developed. The next HAART regimen must be constructed carefully to account for this potential resistance. Where available, ARV resistance testing is strongly recommended to help guide the design of the second-line regimen. If a resistance-testing assay is not available, empiric reasoning regarding the likelihood of resistance to agents in the initial regimen, as well as considerations of cross-resistance, can be used to design a second-line regimen with the highest likelihood of efficacy. Because the exact nature and extent of resistance is difficult to estimate empirically, these guidelines suggest trying to replace as many of the agents in the initial regimen as possible.

Resistance to 3TC and to NNRTIs commonly develops in patients who fail initial treatment regimens containing these agents. Hence, second-line regimens for patients who initiated an NNRTI-based regimen generally involve replacement of the NNRTI with a PI.* Conversely, initial PI-based regimens should generally be replaced with NNRTI-based regimens.

Most initial HAART regimens will also contain either AZT or d4T. Unfortunately, AZT and d4T share similar resistance patterns, and a high degree of cross-resistance between these two drugs limits the utility of replacing one of them with the other. Hence, for patients failing AZT- or d4T-containing HAART regimens, the best second-line options include a nucleoside backbone of ddI plus ABC. Unfortunately, ABC is not universally available in the Caribbean. Fortunately, AZT and d4T will often retain at least partial efficacy in a second-line regimen, because typically HIV must develop multiple resistance mutations before achieving full resistance to either of these agents. Hence, where ABC is not available, AZT or d4T may be used in second-line regimens. The use of TDF cannot be recommended due to insufficient data regarding its use in paediatric patients.

Table 6: Second-Line Regimen Recommendations for Treatment Failure

FAILED FIRST-LINE REGIMEN	SECOND-LINE REGIMEN OPTIONS [†]	COMMENTS
d4T + 3TC + EFV or d4T + 3TC + NVP	ABC + ddI + PI/r [§] or AZT + ddI + PI/r or Substitute NFV for PI/r in above options	<ul style="list-style-type: none"> • ABC not widely available; beware of ABC hypersensitivity • Potency questionable due to cross-resistance between d4T and AZT • PI/r favoured over NFV due to higher potency
AZT + 3TC + EFV or AZT + 3TC + NVP	ABC + ddI + PI/r or AZT + ddI + PI/r or ABC + ddI + AZT + PI/r or Substitute NFV for PI/r in above options	<ul style="list-style-type: none"> • ABC not widely available; beware of ABC hypersensitivity • Potency questionable • Higher pill burden and risk of toxicity • PI/r favoured over NFV due to higher potency
AZT + 3TC + ABC	ABC + ddI + (EFV or NVP) or ABC + ddI + PI/r or ABC + ddI + NFV or Substitute d4T for ABC in above options	<ul style="list-style-type: none"> • Potency questionable; ABC may still retain some activity • PI/r favoured over NFV due to higher potency • d4T + ddI combination not generally recommended due to excess toxicity

* LPV/r is the preferred PI in this circumstance given its high potency and established paediatric dosing and formulation. The use of PIs other than LPV/r and NFV is more problematic in children because of a lack of suitable paediatric drug formulations for IDV and SQV and a lack of appropriate dosing information for RTV-boosted PIs other than LPV/r. However, SQV/r maybe considered as an alternative in children who weigh 25kg or more, and can therefore receive the adult dosage.

[†] 3TC may be added to any of the above regimens. Some expert clinicians suggest continuing 3TC therapy even for patients in whom 3TC resistance is likely, due to reduced replicative capacity (*viral fitness*) induced by the signature 3TC resistance mutation.

[§] PI/r = RTV-boosted PI (LPV/r or, for children >25 kg, SQV/r)

2 NRTIs + (PI or PI/r)	2 different NRTIs + (EFV or NVP) or 2 different NRTIs + PI/r	<ul style="list-style-type: none"> • See patterns above for NRTI selection • Because PI resistance develops relatively slowly, an PI/r-based second-line therapy may be effective even for patients who failed initial PI-based therapy
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SALVAGE THERAPY

Following failure of two or more ARV regimens, durable virologic suppression is unlikely. However, prevention of further immunologic deterioration is possible even in the absence of full virologic suppression. Studies in adults have demonstrated that highly treatment-experienced patients, including those with demonstrably high levels of ARV resistance, generally fare better clinically if they remain on HAART than if they discontinue antiretroviral therapy altogether. Hence, while full virologic suppression may not be a realistic goal for highly treatment-experienced patients, attempts should be made to construct a regimen that will still maintain some efficacy and hopefully prevent or slow further progression of HIV disease. The design of salvage therapy regimens is exceedingly complex and should be performed in consultation with an expert HIV clinician.

PAEDIATRIC ANTIRETROVIRAL THERAPY DRUG FORMULARY FOR THE CARIBBEAN

Based on the recommendations outlined above, nine ARV single drugs and two combination preparations are recommended for consideration for the Paediatric ART Drug Formulary for the Caribbean (*Table 7*).

Table 7: Paediatric ART Drug Formulary for the Caribbean

DRUG CLASS	GENERIC NAME	TRADE NAME	ABBREVIATION
Nucleoside Reverse Transcriptase Inhibitor (NRTI)	Zidovudine	Retrovir ^{®*}	AZT or ZDV
	Lamivudine	Epivir ^{®**}	3TC
	Stavudine	Zerit [®]	d4T
	Didanosine	Videx [®] , Videx [®] EC	ddI
	Abacavir	Ziagen [®]	ABC
Non-Nucleoside Reverse Transcriptase Inhibitor (NNRTI)	Nevirapine	Viramune [®]	NVP
	Efavirenz	Sustiva [®] ; Stocrin [®]	EFV or EFZ
Protease Inhibitor (PI)	Nelfinavir	Viracept [®]	NFV
	Lopinavir/ritonavir	Kaletra [®]	LPV/r

*Also available as Combivir[®] (ZDV/3TC)

**Also available as Trizivir[®] (ZDV/3TC/ABC)

APPENDIX A: CONSIDERATIONS ON SPECIFIC DRUGS

TASTE: There are no good-tasting ARV drugs; RTV and RTV-containing formulations are the worst. NFV tablets dissolve easily in water for ease of administration. The paediatric formulation of NFV is a non-palatable powder.

DOSING: Regimes should be simple, i.e. once or twice-daily. When initiating treatment with NVP, it is administered once daily for two weeks, and if no reaction occurs, then it should be stepped up to twice daily. Discontinue NVP if there is a grade 2 rise in AST and/or ALT.

COMBINATIONS: AZT *plus* d4T in any combination is not recommended due to antagonism of these drugs *in vivo*. Dual or monotherapy with just one or two ARVs is also discouraged. HAART is recommended for all infants, children, and adolescents who are treated with ARV agents, because HAART affords the best opportunity to preserve immune function and delay disease progression. Considerations related to the choice of initial HAART regimens should include an understanding of barriers to adherence, including the complexity of schedules and food requirements for different regimens, as well as palatability problems and potential limitations in subsequent treatment options should resistance develop.

MONITORING AND FOLLOW-UP: It is recommended that all children be seen on a monthly basis, both to monitor for general well-being and toxicity and to encourage adherence. Blood work, including CBC with differential, LFTs, creatinine, and amylase, should be performed one month after initiating treatment and then at three monthly intervals (beginning at three months after commencing treatment). CD4+ T cell counts (percent and absolute) and viral load should be done at three-month intervals, if accessible and available.

TOXICITY: In general, (see toxicity table in *Appendix B*), grade 1 and 2 anomalies are monitored, while grade 3 and 4 toxicities are indications to discontinue the responsible ARV. In some situations, this may mean discontinuing all ARVs until resolution of the abnormality. The most common toxicity is usually AZT-induced anaemia or neutropaenia. In rare cases, there is a rapid drop in haemoglobin, which may be life-threatening, within the first two to four weeks after starting AZT. NRTIs, particularly d4T, ddI, and (to a lesser extent) AZT and 3TC, may cause mitochondrial toxicity. This should be considered especially in a patient presenting with multi-organ dysfunction and/or CNS signs. Elevated ALT or rash (particularly Stevens-Johnson syndrome) is of particular concern in relation to NVP.

TREATMENT FAILURE: The most common cause of treatment failure is nonadherence (poor compliance) with the treatment regime; every effort should be made to confirm that medications are being taken as prescribed prior to any change of therapy for failure. Directly observed therapy (DOT) is strongly recommended as an interventional strategy to facilitate success.

Since a significant proportion of the children may be orphans and cared for by grandparents or elderly guardians, attention should also be paid to the health and well-being of the guardian with particular reference to their eyesight.

SPECIAL PROBLEMS OF CHILDHOOD

GROWTH AND DEVELOPMENT are of paramount importance to the paediatric patient. Even though the child who is nonadherent may have normal growth and development, the failure of these parameters is usually indicative of poor virologic control. The Growth Chart and noting of the Tanner Score are important tools in the care of the paediatric patient.

DISCLOSURE is also an important aspect of care because as children approach adolescence, they participate more in their own care. Their understanding of their condition can make all the difference

between treatment success and failure. It also makes them aware of their parents' diagnoses and subsequent needs to be handled with appropriate sensitivity.

The issue of disclosure is also important in the emerging sexuality of the paediatric patient to control the spread of infection.

Although awareness of HIV has resulted in drastic improvements in care, *STIGMA* and *SEVERE POVERTY* remain major causes of poor adherence. Many patients refuse to be seen at clinics and will not allow healthcare workers to visit their homes. Most liquid ARVs require refrigeration, and this can pose problems since many families do not own refrigerators and some may not want other household members to know that their child is on medication. The healthcare team must be aware of such issues and be willing to devise innovative approaches to the delivery of care to achieve success.

PROGNOSIS

Children treated optimally with HAART, OI prophylaxis, nutritional, and other supportive therapy can grow up to lead normal adult lives. In developed countries, such children are now growing up to consider university educations, buying a house, marrying, and even having children. The long-term prognoses of paediatric HIV/AIDS can therefore be excellent.

APPENDIX B: CURRENTLY AVAILABLE ARVs FOR PAEDIATRIC USE^{§§§}

Table 8: Nucleoside Reverse Transcriptase Inhibitors (NsRTIs) (Part 1 of 2 tables on NsRTIs)*

PART 1 OF 2	ABACAVIR	DIDANOSINE
SHORT FORM	ABC	ddI, ddI EC
TRADE NAME	Ziagen [®] , Trizivir [®] (GW)	Videx [®] , Videx EC [®] (BMS)
PAEDIATRIC DOSE* Do not exceed the recommended adult dose.	Paediatric (age >90 days): 8mg/kg/dose po b.i.d ¹ Neonate (age 30-90 days) (investigational): 8mg/kg/dose po b.i.d ¹	Paediatric¹ (age >90 days): 120mg/m²/dose po b.i.d <i>Range:</i> 90-150mg/m ² /dose po b.i.d (higher doses if risk of CNS disease, especially in young children with developmental delay). Paediatric Enteric-Coated Capsules: 240mg/m ² /dose po q.d ¹² Neonate (age <90 days):¹ 50mg/m ² /dose po b.i.d
ADOLESCENT & ADULT DOSE	300mg po b.i.d	<60kg: 125mg b.i.d ^{1,2} EC: 250mg q.d or 125mg b.i.d ² ≥60kg: 200mg b.i.d ^{1,2} EC: 400mg q.d or 200mg b.i.d ² Use 2 buffered tablets/dose
CANADIAN AVAILABLE FORMS⁶ & STORAGE	300mg tablet room temperature, prescription vial 20mg/mL solution 240mL sorbitol, banana-strawberry flavoured room temperature, Rx bottle Trizivir [®] film-coated tablet (ABC, 300mg + 3TC, 150mg + AZT, 100mg)	25mg, 50mg, 100mg, 150mg chewable-buffered tablets, room temp, Rx vial (60/bottle) 125mg, 200mg, 250mg, 400mg enteric-coated beadlets capsules (EC) (contains no antacid component) (30/bottle) Oral solution 10mg/mL (4g/400mL). Add 200mL water. Shake well, then add 200mL antacid (also available as 2g/200mL). Oral solution 20mg/mL (clinical investigative drug) - 4g/200mL. Loosen powder in bottle. Add 100mL antacid and shake gently for 1 minute. Add 100mL antacid and shake gently for 1 more minute. ¹¹ 30 days, refrigerated, shake well, glass bottle Antacid = Mylanta Double Strength, Maalox TC, or Maalox Plus ES (cherry-flavoured, saccharin) ⁵ (other antacids in product monograph)

^{§§§}All pharmaceutical charts in *Appendix IX-B* were graciously authored and contributed by Natalie Dayneka, B.Sc.Pharm., PharmD, Clinical Specialist, Children’s Hospital of Eastern Ontario, Ontario, Canada.

PART 1 OF 2	ABACAVIR	DIDANOSINE
MAIN PRECAUTION	Potentially fatal hypersensitivity ± rash (3.7% of children and adults) usually within first 6 weeks (1-2 weeks most common). ³ Signs include: flu-like symptoms, fever, shortness of breath, maculopapular or urticarial rash, fatigue, nausea and vomiting, diarrhoea, and abdominal pain. Do not restart: life-threatening hypotension and death can occur in hours.	Pancreatitis (less common in paediatrics) ¹ , peripheral neuropathy
TOXICITY	<p>More Common: Nausea, vomiting, fever, rash (maculopapular or urticarial)³, anorexia, diarrhoea</p> <p>Less Common (more severe):¹ Potentially fatal hypersensitivity reaction, ↑ CPK, ↑ Cr, lymphopaenia</p> <p>Rare:¹ Pancreatitis, ↑ LFTs, ↑ glucose, ↑ TRIG</p> <p>ADRs for NRTI Class:² Lactic acidosis and severe hepatomegaly with hepatic steatosis - rare, but may be fatal; discontinue all NRTIs if ↑↑ LFTs</p> <p>Sorbitol: abdominal pain, diarrhoea</p>	<p>Paediatric ADR Rates⁵:</p> <p>More Common¹: Diarrhoea 81%, abdominal 35%, nausea and vomiting 58%, chills/fever 82%</p> <p>Less Common (more severe):¹ Peripheral neuropathy (dose related),</p> <p>↑↓ electrolytes, ↑ uric acid</p> <p>Rare:¹ Pancreatitis 7% (dose-related, less common in paediatrics, can be fatal, ↑ with d4T), ↑ LFTs 38%, retinal depigmentation</p> <p>ADRs for NRTI Class:² Lactic acidosis and severe hepatomegaly with hepatic steatosis - rare but may be fatal; discontinue all NRTIs if ↑↑ LFTs.</p>
MONITORING (blood tests)	ALT, amylase, TRIG, ^{8,9} CHOL, ^{8,9} glucose, ^{8,9} lactate, Cr, CBC with Diff, creatine phosphokinase (CPK)	ALT, amylase, electrolytes, uric acid, lactate, TRIG, ^{8,9} CHOL, ^{8,9} glucose, ^{8,9} aluminium (only with oral liquid)
DRUG INTERACTIONS		<ul style="list-style-type: none"> • Avoid co-administration with other drugs known to cause peripheral neuropathy (d4T, ddC) or pancreatitis (d4T, ddC, 3TC, RTV)² • Take 2 hours BEFORE ddI: dapsone, azole antifungals, H₂ blockers, fluoroquinolones, ganciclovir, TFV (↓ dose), RTV, (all drugs altered by antacid of buffered tablets) • Take 1 hour BEFORE ddI: tetracyclines, iron salts, NFV
MARKET STATUS ⁶⁺	Marketed (tablets/liquid)	Marketed (tablets/EC tablets), SAP – Sunnybrook (oral solution)
DOSE IN ORGAN FAILURE	↓ dose in hepatic dysfunction	↓ dose if CrCl <60mL/min HD: Drug removed (supplement dose not required) Liver disease: ↓ dose

PART 1 OF 2	ABACAVIR	DIDANOSINE
CSF/PLASMA BIOAVAILABILITY HALF-LIFE	27-33% ⁷ F = 0.83 ² t _{1/2c} = 12-26h ² , t _{1/2} = 1.5h ²	Adult 21% ⁷ , child mean 46% ⁷ F = 0.3-0.4 ² t _{1/2c} = >20h ² , t _{1/2} = 1.5h ²
MEALS	May take with or without food	Adults: Do not give with food; Children: May take with food ¹⁰
SPECIAL INSTRUCTIONS	<ul style="list-style-type: none"> • Watch for rash • Manufacturer provides hypersensitivity warning card for patient 	<p>Buffered Tablets:</p> <ul style="list-style-type: none"> • 2 tablets/dose (do not swallow whole) • Chew tablets; crush or add 2 tablets to ≥30mL cold water for 10 minutes, then stir, may then add ≤30mL clear apple juice (stable for 1 hour at room temperature once mixed)⁵ • Do not give with other fruit juices, acidic drinks, or feeds • Adults: Do not give with >60mL milk • Adults: Give at least 30 minutes before meal or 2 hours after^{2,5} • Children: May take with milk or food (one published study)¹⁰ • Separate from other medications by ≥2 hours <p>Enteric-Coated Capsules:</p> <ul style="list-style-type: none"> • Swallow whole

Note: *Do not exceed the recommended adult dose. Some information in this chart may be at variance with the product monograph. Please consult current recommendations before using this chart.

[†]Market status does not imply approval for paediatric use.

Table 9: Nucleoside Reverse Transcriptase Inhibitors (NsRTIs) (Part 2 of 2 tables on NsRTIs)*

PART 2 OF 2	LAMIVUDINE	STAVUDINE	ZALCITABINE	ZIDOVUDINE
SHORT FORM	3TC	d4T	ddC	ZDV, AZT
TRADE NAME	3TC [®] , Heptovir [®] (GW) (EpiVir [®] US)	Zerit [®] (BMS)	Hivid [®] (Roche)	Retrovir [®] , Combivir [®] , Trizivir [®] (GW)
PAEDIATRIC DOSE* Do not exceed the recommended adult dose.	Paediatric: ¹ 4mg/kg/dose po b.i.d Neonate (<age 30 days): ¹ 2mg/kg/dose po b.i.d	Paediatric: ¹ 1mg/kg/dose po b.i.d up to 30mg po b.i.d Neonate (PACTG 332): ¹ Unknown Adult: ¹ For Zerit [®] extended-release (ER) 75 & 100mg capsules (not available in Canada) ≥60kg: 100mg po q24h <60kg: 75mg po q24h	Paediatric: ¹ 0.01mg/kg/dose po q8h	Paediatric ¹ : po: 180mg/m ² /dose b.i.d 160mg/m ² /dose q8h <i>Range:</i> 90-180mg/m ² /dose q6-8h IV: 120mg/m ² /dose q6h or 20mg/m ² /hour <hr/> Perinatal Exposure: 8-12 hours after birth for 6 weeks ⁴ Neonate (term to age 90 days): ¹ 2mg/kg/dose po q6h 1.5mg/kg/dose IV q6h Premature (<35 weeks): ^{1,4} 2mg po q12h or 1.5mg/kg/dose IV q12h <30 Weeks GA: ↑ q8h after 4 weeks ≥30 Weeks GA: ↑ q8h after 2 weeks
ADOLESCENT & ADULT DOSE	≥50kg: 150mg po b.i.d or 300mg po q.d ²	≤60kg: 30mg po b.i.d ^{1,2} >60kg: 40mg po b.i.d ^{1,2}	0.75mg po t.i.d ^{1,2}	200mg t.i.d or 300mg b.i.d ^{1,2}

PART 2 OF 2	LAMIVUDINE	STAVUDINE	ZALCITABINE	ZIDOVUDINE
<p>CANADIAN AVAILABLE FORMS⁶ & STORAGE</p>	<p>1) 150mg white film-coated tablet (not scored – may cut in half) (60/bottle)</p> <p>2) Oral solution: 10mg/mL 240mL strawberry-banana (20% sucrose) Rx bottle, room temperature</p> <p>3) 300mg tablet (30/bottle)</p> <p>4) Combivir[®] film-coated tablet (3TC, 150mg + AZT, 100mg)</p> <p>5) Trizivir[®] film-coated tablet (ABC, 300mg + 3TC, 150mg + ZDV, 100mg)</p> <p>For Hepatitis B: Heptovir[®], 100mg tablet (60/bottle) (not scored - may cut in half) 5mg/mL strawberry-banana (no alcohol)</p>	<p>15mg, 20mg, 30mg, and 40mg capsules: Rx vial, room temperature</p> <p>Liquid: 1mg/mL fruit-flavoured (clinical investigational drug) 2g/200mL. Shake well, refrigerate, 30-day expiry</p>	<p>0.375mg and 0.75mg film-coated tablets</p> <p>0.1mg/mL syrup, 30mL (clinical investigative drug) room temperature, original bottle (glass)</p>	<p>1) 100mg capsule, Rx vial, room temperature</p> <p>2) 10mg/mL syrup, 240mL strawberry-flavoured, Rx bottle, room temperature</p> <p>3) 10mg/mL injection--20mL vial</p> <p>IV: Over 1 hour NS or D5W</p> <p>≤4mg/mL, 8-hour expiry at room temperature, 24-hour expiry in refrigerator</p> <p>4) Combivir[®] film-coated tablet (3TC, 150mg + AZT, 100mg)</p> <p>5) Trizivir[®] film-coated tablet (ABC, 300mg + 3TC, 150mg + AZT, 100mg)</p>
<p>MAIN PRECAUTION</p>	<p>Pancreatitis</p>	<p>Peripheral neuropathy, pancreatitis</p>	<p>Peripheral neuropathy, pancreatitis</p>	<p>Myelosuppression, severe anaemia</p>

PART 2 OF 2	LAMIVUDINE	STAVUDINE	ZALCITABINE	ZIDOVUDINE
TOXICITY	<p>More Common:¹ HA, fatigue, nausea, diarrhoea, rash, abdominal pain</p> <p>Less Common (more severe):¹ Pancreatitis 14% (seen in paediatric advanced HIV on multiple medications),⁵ paresthaesia/peripheral neuropathy 15%,⁵ ↓ WBC (neutrophils), ↑ LFTs</p> <p>ADRs for NRTI Class:² Lactic acidosis and severe hepatomegaly with hepatic steatosis - rare but may be fatal. Discontinue all NRTIs if ↑↑ LFTs</p>	<p>More Common:¹ Headache, GI disturbances, rash</p> <p>Less Common (more severe):¹ Peripheral neuropathy (7-21%),⁵ pancreatitis</p> <p>Rare:¹ ↑ LFTs</p> <p>ADRs for NRTI Class:² Lactic acidosis and severe hepatomegaly with hepatic steatosis - rare but may be fatal. Discontinue all NRTIs if ↑↑ LFTs</p> <p>d4T ↑ risk of lactic acidosis compared to other NRTIs² (discontinue stat if lactate >10mmol/L, interrupt NRTI therapy if 5–10mmol/L)</p>	<p>More Common:¹ Headache, GI disturbances, malaise</p> <p>Less Common (more severe):¹</p> <ul style="list-style-type: none"> • Peripheral neuropathy (↑ rate in children) • Pancreatitis, hepatic toxicity, oral ulcers, oesophageal ulcers, rashes, ↓ platelets, ↓ WBC, ↓ Hgb <p>ADRs for NRTI Class:² Lactic acidosis and severe hepatomegaly with hepatic steatosis - rare but may be fatal. Discontinue all NRTIs if ↑↑ LFTs</p>	<p>More Common:¹ Haematologic toxicity (↓ WBC, ↓ Hgb, ↓ PLT), headache, nausea and vomiting</p> <p>Less Common (more severe):¹ Myopathy, myositis, liver toxicity</p> <p>Bone Marrow Suppression:⁵ (Neutropaenia ± anaemia)</p> <p>↓ WBC: Mean onset 6 -8 weeks Tx: G-CSF</p> <p>↓ Hgb: Dose-related--mean onset 4-6 weeks, as early as 2 weeks Tx: EPO</p> <p>ADRs for NRTI Class:² Lactic acidosis and severe hepatomegaly with hepatic steatosis - rare but may be fatal. Discontinue all NRTIs if ↑↑ LFTs</p>
MONITORING (blood tests)	CBC, ALT, amylase, lactate, TRIG, ^{8,9} CHOL, ^{8,9} glucose ^{8,9}	ALT, amylase, TRIG, ^{8,9} CHOL, ^{8,9} glucose ^{8,9}	CBC, ALT, amylase, TRIG, ^{8,9} CHOL, ^{8,9} glucose ^{8,9}	CBC (retic count, MCV), ALT, amylase, lactate, TRIG, ^{8,9} CHOL, ^{8,9} glucose ^{8,9}
DRUG INTERACTIONS	<ul style="list-style-type: none"> • TMP-SMX may ↑ 3TC levels (↓ renal tubular secretion) (significance???) • 3TC may prevent AZT resistance¹ 	<ul style="list-style-type: none"> • INH, metronidazole, dapsone, phenytoin, pentamidine, (avoid co-administration with drugs that ↑ risk of peripheral neuropathy) • ddI (avoid co-administration with drugs that ↑ risk of pancreatitis, peripheral neuropathy, ↑ LFTs)⁵ • AZT (↓ effect)¹ 	<ul style="list-style-type: none"> • Ampho B, gentamicin, foscarnet (↓ renal elimination) • ddI (avoid co-administration with drugs that ↑ risk of peripheral neuropathy) • Pentamidine (↑ pancreatitis) • Antacids (↓ absorption) 	<ul style="list-style-type: none"> • -Acyclovir, ganciclovir, interferon α, β, and β1A (bone marrow suppression) • RIF, rifabutin (↓ AZT) • Clarithromycin (4 hours apart) (↓ AZT absorption) • Fluconazole (74% ↑ AZT),

PART 2 OF 2	LAMIVUDINE	STAVUDINE	ZALCITABINE	ZIDOVUDINE
				methadone, atovaquone, valproic acid, phenytoin, probenecid (inhibit glucuronidation) • d4T (↓ effect) ¹
MARKET STATUS⁶⁺	Marketed (tablets, liquid)	Liquid and extended-release capsules not marketed in Canada	Syrup not marketed	300mg tablet not marketed in Canada
DOSE IN ORGAN FAILURE	↓ dose if CrCl mL/min ² : 30-49: 150mg po q24h 15-29: 150mg x 1, 100mg po q24h 5-14: 150mg x 1, 50mg po q24h <5 & HD: 50mg x 1, 25mg po q24h	↓ 30-40mg dose if CrCl mL/min ² : 26-50: 15-20mg q12h 10-25: 15-20mg q24h HD: Dose for CrCl 10-25mL/min and give after dialysis	↓ frequency if CrCl mL/min ² : 10-40: q12h <10: q24h Liver Disease: Caution	↓ dose if CrCl <30mL/min ² : HD: 100mg po t.i.d Hgb <80 g/L: ↓ dose 30% Liver disease: ↓ dose
CSF/PLASMA BIOAVAILABILITY HALF-LIFE	6-31% ⁷ F = 0.86 ² t _{1/2c} = 18-22h ² , t _{1/2} = 5-7h ²	Child 59% ⁷ F = 0.86 ² t _{1/2c} = 7.5h ² , t _{1/2} = 1h ²	9-37% (mean 20%) ⁷ F = 0.85 ² t _{1/2} = 1.2h ²	Child 68% ⁷ F = 0.6 ² , t _{1/2c} = 7h ² t _{1/2} adult = 1.1h ² , t _{1/2} neonate = 3.1h ⁴ t _{1/2} prem (26-33 wk) = 7.2h ⁴
MEALS	Take with or without food	Take with or without food	Take with or without food ²	Take with or without food ^{1,2}
SPECIAL INSTRUCTIONS	<ul style="list-style-type: none"> • If 3TC upsets the stomach, take with food • May cut tablet in half • May crush tablet 	<ul style="list-style-type: none"> • If d4T upsets the stomach, take with food • May open capsule and give in small portion of food or 5-10mL cool tap water 	<ul style="list-style-type: none"> • If ddC upsets the stomach, take with food 	<ul style="list-style-type: none"> • Manufacturer recommends 30 minutes before meals or 1 hour after, but OK to take with food • If AZT upsets the stomach, take with food • May open capsule and give in small portion of food or 5-10mL cool tap water

Note:

*Do not exceed the recommended adult dose. Some information in this chart may be at variance with the product monograph. Please consult current recommendations before using this chart.

[†]Market status does not imply approval for paediatric use.

References:

¹US DHHS. Guidelines for the use of antiretroviral agents in pediatric HIV infection. 30 Nov 2004 revision. Last accessed 30 Nov 2004. Available at: <<http://AIDSinfo.nih.gov>>.

²US DHHS. Guidelines for the use of antiretroviral agents in HIV-infected adults and adolescents. 29 Oct 2004 revision. Last accessed 29 Oct 2004. Available at: <<http://AIDSinfo.nih.gov>>.

³US DHHS. Supplement I: pediatric antiretroviral drug information in Guidelines for the use of antiretroviral agents in pediatric HIV infection. 30 Nov 2004 revision. Last accessed 30 Nov 2004. Available at: <<http://AIDSinfo.nih.gov>>.

⁴US DHHS. Public health service task force recommendations for the use of antiretroviral drugs in pregnant women infected with HIV-1 for maternal health and interventions to reduce perinatal HIV-1 transmission in the United States. 17 Dec 2004 revision. Last accessed 17 Dec 2004. Available at: <<http://AIDSinfo.nih.gov>>.

⁵Compendium of Pharmaceuticals and Specialties. Ottawa:Canadian Pharmacists Association; 2004.

⁶Drug Product Database [database on the Internet]. Ottawa:Health Canada. c2004 [cited 21 Jan 2005]. Available at: <http://www.hc-sc.gc.ca/hpb/drugs-dpd>>.

⁷Facts and Comparisons, Nov 2004.

⁸Qaqish RB, Fisher E, Rublein J, Wohl DA. HIV-associated lipodystrophy syndrome. *Pharmacotherapy* 2000;20(1):13-22.

⁹Leonard EG, McComsey GA. Metabolic complications of antiretroviral therapy in children. *Ped Inf Dis J* 2003;(22):77-84

¹⁰Stevens RC et al. and the Pediatric AIDS Clinical Trials Group Protocol 144 Study Team. Effect of food and pharmacokinetic variability on didanosine systemic exposure in HIV-infected children. *AIDS Res & Hum Retrovir* 2000;16(5):415-21.

¹¹Bristol-Myers Squibb personal communication, 25 Jan 2001.

¹²King JR, et al. Single-dose pharmacokinetics of enteric-coated didanosine in HIV-infected children. *Antiviral Ther* 2002;(7):267-270.

Table 10: Nucleotide Reverse Transcriptase Inhibitors (NtRTIs)*

PART 1 OF 1	TENOFIVIR disoproxil fumarate
SHORT FORM	TDF, TFV
TRADE NAME	Viread® (Gilead)
PAEDIATRIC DOSE* Do not exceed the recommended adult dose.	Paediatric: <i>Study Gilead 926:</i> 175mg/m ² /dose po q.d ⁷ <i>Study Gilead 927:</i> Given po q.d ⁷ 10-<20kg: 75mg 20-<35kg: 150mg 35-<50kg: 225mg ≥50kg: 300mg
ADOLESCENT & ADULT DOSE	300mg po q.d ²
CANADIAN AVAILABLE FORMS⁴ & STORAGE	300mg almond-shaped, light-blue film-coated tablet (30/vial with desiccant) original bottle room temperature (not scored - may cut in quarters or half) (Note: Tenofovir DF 300mg = tenofovir D 245mg)
MAIN PRECAUTION	Lactic acidosis and severe hepatomegaly
TOXICITY	Most Common: ^{1,2} Nausea, diarrhoea, vomiting, flatulence, asthaenia Rare (animal data only): ¹ Reduced bone density and osteomalacia; renal toxicity (↑ BU, ↑ Cr, ↓ PO ₄ , glycosuria, proteinuria, phosphaturia, calcuria) ADRs for NtRTI Class: ² Lactic acidosis and severe hepatomegaly - rare, but may be fatal; discontinue all NRTIs and NtRTIs if ↑↑ LFTs
MONITORING (blood tests)	ALT, amylase, TRIG ⁵ , CHOL ⁵ , glucose ⁵ , BU, Cr, serum calcium, serum phosphate, urine analysis (glucose, protein, phosphate, calcium), serum lactate, bone density (annual)
DRUG INTERACTIONS	↑ ddI AUC 44%, ⁶ ↑ddI EC AUC 48%, ⁶ ↓ ATV LPV/RTV: ↑ TFV AUC 34% (no dose adjustment required)
MARKET STATUS⁴⁺	Tablet marketed

PART 1 OF 1	TENOFIVIR disoproxil fumarate
DOSE IN ORGAN FAILURE	↓ dose if CrCl mL/min ² : 30-49: 300mg po q48h 10-29: 300mg po b.i.w ESRD and HD: 300mg po q.w
CSF/PLASMA BIOAVAILABILITY HALF-LIFE	CSF <1% serum concentration (monkey data) ⁸ F = 0.25 (fasting) ² F = 0.39 (high-fat meal) ² t _{1/2C} = >60h, ² t _{1/2} = 17h ²
MEALS	Take with food
SPECIAL INSTRUCTIONS	<ul style="list-style-type: none"> • Bitter taste • Tablets may be split or chewed • May dissolve in water, grape juice, or grapefruit juice. Once dissolved, take immediatelyⁿ • May take on an empty stomach but bioavailability increases when taken with high-fat meal^{1,2} • Give TDF 2 hours before or 1 hour after ddI. • TDF is primarily excreted unchanged (70-80%) by the kidneys via glomerular filtration and active tubular secretion

Note:

*Do not exceed the recommended adult dose. Some information in this chart may be at variance with the product monograph. Please consult current recommendations before using this chart.

[†]Market status does not imply approval for paediatric use.

References:

¹US DHHS. Guidelines for the use of antiretroviral agents in pediatric HIV infection. 30 Nov 2004 revision. Last accessed 30 Nov 2004. Available at: <<http://AIDSinfo.nih.gov>>.

²US DHHS. Guidelines for the use of antiretroviral agents in HIV-infected adults and adolescents. 29 Oct 2004 revision. Last accessed 29 Oct 2004. Available at: <<http://AIDSinfo.nih.gov>>.

³US DHHS. Supplement I: pediatric antiretroviral drug information in Guidelines for the use of antiretroviral agents in pediatric HIV infection. 30 Nov 2004 revision. Last accessed 30 Nov 2004. Available at: <<http://AIDSinfo.nih.gov>>.

⁴Drug Product Database [database on the Internet]. Ottawa, Canada:Health Canada. c2004 [cited 21 Jan 2005]. Available at: <http://www.hc-sc.gc.ca/hpb/drugs-dpd>>.

⁵Qaqish RB, Fisher E, Rublein J, Wohl DA. HIV-associated lipodystrophy syndrome. *Pharmacotherapy* 2000;20(1):13-22.

⁶Gilead Sciences. Viread[®] (tenofovir). Product monograph, October 2003. Last accessed 2004. Available at <http://www.gilead.com/pdf/viread_pi.pdf>.

⁷Written Communication, Tenofovir DF (Viread[®]) in HIV-Infected Pediatric Patients, Gilead Sciences, Inc. 27 May 2003.

⁸Verbal Communication, Gilead Sciences, Inc., 19 Aug 2003.

Table 11: Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)

PART 1 OF 1	DELAVIRDINE	EFAVIRENZ	NEVIRAPINE
SHORT FORM	DLV	EFV	NVP
TRADE NAME	Rescriptor [®] (Agouron)	Sustiva [®] (DUP)	Viramune [®] (BOE)
PAEDIATRIC DOSE* Do not exceed the recommended adult dose.	Unknown	Paediatric (>age 3 years):¹ Give q.d. 10-<15kg: 200mg 15-<20kg: 250mg 20-<25kg: 300mg 25-<32.5kg: 350mg 32.5-<40kg: 400mg ≥40kg: 600mg	Paediatric Starting Dose:¹ 120mg/m ² /dose po q.d for 14 days, then 120mg/m ² /dose po b.i.d if no rash or ADR <i>Range (if no rash or ADR):</i> 120-200mg/m ² /dose po b.i.d OR <Age 8 Years: 7mg/kg/dose po b.i.d >Age 8 Years: 4mg/kg/dose po b.i.d Neonate (<age 2 months) (PACTG 365):¹ 5mg/kg/dose or 120mg/m ² /dose po q.d for 14 days, THEN 120mg/m ² /dose po b.i.d for 14 days, THEN 200mg/m ² /dose po b.i.d Newborn Prophylaxis:⁴ Mother, 200mg po x 1 at onset of labour; baby 2mg/kg/dose po x 1 at 48-72 hours (if mother given dose <1 hour before delivery, baby requires 2 doses (1 stat and 2 at 48-72 hours))
ADOLESCENT & ADULT DOSE	400mg po t.i.d 600mg po b.i.d ¹ (investigational)	600mg po q.d (qhs) (may give 300mg po b.i.d to decrease dizziness)	200mg po q.d for 14 days then if no rash, 200mg po b.i.d
CANADIAN AVAILABLE FORMS⁶ & STORAGE	100mg white, film-coated, capsule-shaped tablet Room temperature, Rx vial	50mg, 100mg, and 200mg capsules; Rx vial, room temperature Oral liquid (clinical investigative drug)	200mg scored tablet (60/bottle), (may cut in half), room temperature, Rx vial 10mg/mL syrup (240mL bottle), sweet-flavoured (clinical investigative drug), room temperature, shake well, original bottle (but CHEO uses glass bottle)

PART 1 OF 1	DELAVIRDINE	EFAVIRENZ	NEVIRAPINE
MAIN PRECAUTION	Rash	Rash	Rash, hepatitis
TOXICITY	<p>More Common:¹ Headache, fatigue, vomiting, rash</p> <p>Dermatologic:⁵ Rash may develop 1-3 weeks after starting DLV; resolves 3-14 days without changing dose. Stevens-Johnson syndrome reported. Discontinue DLV if rash plus fever, blistering, oral lesions, conjunctivitis, swelling, muscle or joint pain.</p> <p>ADRs for NNRTI Class:¹ Rash - (can be severe. Potentially fatal cases of Stevens-Johnson syndrome have been reported).</p>	<p>More Common:^{1,3} Skin rash:</p> <ul style="list-style-type: none"> • maculopapular and pruritic ($\leq 40\%$ incidence in children compared to 27% in adults) • usual onset first 2 weeks of therapy • usually do not need to discontinue EFV • CNS (somnolence, insomnia, abnormal dreams, confusion, abnormal thinking, agitation, impaired concentration, amnesia, depersonalisation, hallucinations, euphoria) (50% adults compared to 14% children) • \uparrow LFTs <p>Teragenic in primates: 1) do not use in pregnancy 2) caution in females with child-bearing potential</p> <p>ADRs for NNRTI class:¹ Rash - (can be severe. Potentially fatal cases of Stevens-Johnson syndrome have been reported).</p>	<p>More Common:¹ Skin rash (can be severe and life-threatening, including Stevens-Johnson syndrome, toxic epidermal necrolysis), fever, headache, diarrhoea, nausea, \uparrow LFTs</p> <p>Less Common:¹ Hepatitis (most cases of severe and life-threatening skin reactions and/or serious hepatitis/hepatic failure have occurred within the first 6-8 weeks of starting NVP⁵)</p> <p>Rash:⁵ Maculopapular, erythematous \pm itching 16%, severe or life-threatening rash 6.6% Discontinue immediately and do not restart after:⁵ \uparrow LFTs with rechallenge, clinical hepatitis, severe rash, hypersensitivity (rash + fever/artralgias + organ dysfunction including eosinophilia, granulocytopenia)</p> <p>ADRs for NNRTI Class:¹ Rash - (can be severe. Potentially fatal cases of Stevens-Johnson syndrome have been reported).</p>
MONITORING (blood tests)	CBC, (frequent ANC if also on NFV), ALT, CPK, amylase, Cr, TRIG, ^{5,9} CHOL ^{5,9}	CBC, ALT, TRIG, ^{5,9} CHOL ^{5,9}	CBC, ALT, electrolytes, glucose, Cr [Monitor closely (b.i.w.) first 12 weeks of therapy], TRIG, ^{5,9} CHOL ^{5,9}
DRUG INTERACTIONS	<p><u>Inhibits CYP3A</u></p> <p>DLV \uparrow concentration of:^{1,5} SQV, RTV, IDV, NFV, APV, LPV/RTV, clarithromycin, voriconazole</p> <p>\uparrow concentration of DLV: ketoconazole, fluoxetine, clarithromycin, voriconazole</p> <p>Do not use with:^{2,5}</p> <ul style="list-style-type: none"> • (\uparrow concentration of DLV) alprazolam, 	<p><u>Mixed inducer/inhibitor of P450 CYP 3A4</u></p> <p>Do not use with:² Midazolam, triazolam, ergot alkaloids, cisapride, St. John's wort,¹⁰ voriconazole</p> <p>Use with caution: Warfarin, ethinyl estradiol (use additional method of birth control)</p> <p>EFV \uparrow concentration of:^{1,2} RTV and EFV(\uparrow 20%), NFV (\uparrow 20%)</p>	<p><u>Auto-induction occurs in 2-4 weeks (1.5-2xs \uparrow in clearance¹)</u></p> <p><u>Induces P450 CYP 3A and CYP 2B (may need to \uparrow dose of other drugs metabolised by P450 enzymes in the liver)</u></p> <p>Do not use with:² Ketoconazole, RIF, St. John's wort¹⁰</p> <p>\uparrow concentration of:¹ SQV, IDV, LPV/r, ATV</p>

PART 1 OF 1	DELAVIRDINE	EFAVIRENZ	NEVIRAPINE
	<p>midazolam, triazolam, ergot alkaloids, simvastatin, lovastatin, H-2 blockers, proton pump inhibitors, cisapride</p> <ul style="list-style-type: none"> (↓ concentration of DLV) RIF, rifabutin, phenytoin, carbamazepine, phenobarb, St. John's wort¹⁰ 	<p>EFV ↓ concentration of:^{1,2} Clarithromycin (use azithromycin), SQV (↓ 50%), IDV (↓ 31%), NFV, APV (36%), ATV (74%)</p> <p>↓ concentration of EFV:^{1,2} RIF, rifabutin, phenobarb, phenytoin, St. John's wort¹⁰</p>	<p>Caution with¹: Clarithromycin, fluconazole (↑ LFTs), rifabutin, oral contraceptives (use additional methods), digoxin, triazolam, midazolam, warfarin, phenytoin, prednisone (↑ severity of rash during first 6 weeks of starting NVP⁵)</p>
MARKET STATUS ⁶⁺	Marketed	Marketed	CLINICAL INVESTIGATIVE DRUG: liquid
DOSE IN ORGAN FAILURE	Caution with hepatic impairment	Caution with hepatic impairment	Avoid with hepatic impairment
CSF/PLASMA BIOAVAILABILITY HALF-LIFE	<p>0.4%⁷ F = 0.85² t_{1/2} = 5.8h²</p>	<p>0.26-1.19% (av. 0.69%)⁷ F = unknown² t_{1/2} = 40-55h²</p>	<p>0.45%⁷ F = >0.9² t_{1/2} = 25-30h²</p>
MEALS	May take with or without food	May take with or without food but do not take with high fat meal (50% ↓ EFV)	Take on an empty stomach or with food
SPECIAL INSTRUCTIONS	<ul style="list-style-type: none"> Check all medications for drug interaction May dissolve 100mg tablet in 25mL water.² Take immediately. If achlorhydria, take with acidic beverage (orange or cranberry juice) Take 1 hour before or after ddI or antacid² 	<ul style="list-style-type: none"> Peppery taste May open capsule and add to food or liquid Grape jelly can be used to mask taste Give at bedtime during first 2-4 weeks of therapy to ↓ CNS effects When mixed with applesauce, causes burning sensation in mouth 200mg capsule may be mixed in 5mL OraSweet[®] immediately prior to NG tube administration¹¹ 	<ul style="list-style-type: none"> Do not ↑ dose if rash appears within first 14 days If discontinued for >7 days, restart at q.d⁵ Discontinue immediately and contact doctor if: Rash with fever, blistering, oral lesions, conjunctivitis, swelling, muscle or joint aches, or general malaise Contact doctor if: any signs of liver injury (nausea, vomiting, tiredness, loss of appetite, or jaundice) May crush tablets, mix in water and give orally or by G-tube May give at same time as ddI¹

Note: *Do not exceed the recommended adult dose. Some information in this chart may be at variance with the product monograph. Please consult current recommendations before using this chart.

[†]Market status does not imply approval for paediatric use.

References:

¹US DHHS. Guidelines for the use of antiretroviral agents in pediatric HIV infection. 30 Nov 2004 revision. Last accessed 30 Nov 2004. Available at: <<http://AIDSinfo.nih.gov>>.

²US DHHS. Guidelines for the use of antiretroviral agents in HIV-infected adults and adolescents. 29 Oct 2004 revision. Last accessed 29 Oct 2004. Available at: <<http://AIDSinfo.nih.gov>>.

³US DHHS. Supplement I: pediatric antiretroviral drug information in Guidelines for the use of antiretroviral agents in pediatric HIV infection. 30 Nov 2004 revision. Last accessed 30 Nov 2004. Available at: <<http://AIDSinfo.nih.gov>>.

⁴US DHHS. Public health service task force recommendations for the use of antiretroviral drugs in pregnant women infected with HIV-1 for maternal health and interventions to reduce perinatal HIV-1 transmission in the United States. 17 Dec 2004 revision. Last accessed 17 Dec 2004. Available at: <<http://AIDSinfo.nih.gov>>.

⁵Compendium of Pharmaceuticals and Specialties. Ottawa:Canadian Pharmacists Association; 2004.

⁶Drug Product Database [database on the Internet]. Ottawa, Canada:Health Canada. c2004 [cited 21 Jan 2005]. Available at: <http://www.hc-sc.gc.ca/hpb/drugs-dpd>.

⁷Facts and Comparisons, Nov 2004.

⁸Qaqish RB, Fisher E, Rublein J, Wohl DA. HIV-associated lipodystrophy syndrome. *Pharmacotherapy* 2000;20(1):13-22.

⁹Leonard EG, McComsey GA. Metabolic complications of antiretroviral therapy in children. *Ped Inf Dis J* 2003;(22):77-84.

¹⁰Piscitelli SC, Burstein AH, Chait D, et al. Indinavir concentrations and St. John's wort. *Lancet* 2000;355:547-8 [letter].

¹¹Written communication, DuPont, 27 Mar 2001.

Table 12: Protease Inhibitors (PIs) (Part 1 of 3 tables on PIs)*

PART 1 OF 3	AMPRENAVIR	INDINAVIR
SHORT FORM	APV	IDV
TRADE NAME	Agenerase® (GW)	Crixivan® (Merck)
PAEDIATRIC DOSE* Do not exceed the recommended adult dose.	Paediatric (>age 3 years and <50kg):¹ <i>Solution:</i> 22.5mg/kg/dose po b.i.d or 17mg/kg/dose po t.i.d <i>Capsules:</i> 20mg/kg/dose po b.i.d or 15mg/kg/dose po t.i.d Note: <ul style="list-style-type: none"> Do not use in neonates, children <age 4 years, pregnant women¹ (vitamin E & propylene glycol toxicity) Capsules and solution are difficult doses 	Paediatric:¹ 500mg/m ² /dose po q8h <i>Range:</i> 300-500mg/m ² /dose po q8h Neonate: Do not give to neonates due to risk of hyperbilirubinaemia ¹
ADOLESCENT & ADULT DOSE	≥50kg: 1,200mg po b.i.d ^{1,2} (8 x 150mg capsules) 1,400mg po b.i.d (oral solution) Combination Therapy: APV 600mg + RTV 100mg po b.i.d APV 1,200mg + RTV 200mg po q.d	800mg po q8h ² Combination Therapy²: IDV 800mg + RTV 100 or 200mg po b.i.d IDV 1,000mg po t.i.d + EFV 600mg po q.d
CANADIAN AVAILABLE FORMS⁶ & STORAGE	50mg and 150mg soft gelatin capsule (vitamin E 109IU and propylene glycol 57mg per 150mg capsule), room temperature, original bottle Oral solution 15mg/mL vitamin E 46IU/mL, propylene glycol 550mg/mL, PEG400 170mg/mL, tutti-frutti-flavoured, saccharin, room temperature, original bottle	200 and 400mg capsule (powder) room temperature, Capsules OK for 7 days in Rx vial, ¹⁹ dispense in original bottle 10mg/mL glass bottle, refrigerate, 14 days (complex compounding formulation ²⁰)
MAIN PRECAUTIONS	Drug interactions, vitamin E and propylene glycol toxicity	Drug interactions, nephrolithiasis, hyperbilirubinaemia
TOXICITY	More Common:¹ Vomiting, nausea, diarrhoea, perioral paresthesias, rash Less Common (more severe):¹ Life-threatening rash, including Stevens-Johnson syndrome (1%) Rare¹: New onset and exacerbation of pre-existing diabetes mellitus, haemolytic anaemia, ↑ LFTs	More Common:¹ Nausea, abdominal pain, headache, metallic taste, dizziness, asymptomatic hyperbilirubinaemia (10%) (associated with higher doses) Less Common (more severe):¹ Nephrolithiasis (29% in paediatrics vs. 9.8% in adults), ⁵ ↑ chronic liver disease, precipitated IDV (crystalluria) ¹⁵

PART 1 OF 3	AMPRENAVIR	INDINAVIR
	<p>Class ADR PIs:² Hyperglycaemia/diabetes mellitus, ketoacidosis, fat redistribution and lipid abnormalities, hyperlipidaemia, bleeding-haemophilia^{1,2,9}</p> <p>Vitamin E Toxicity:¹ Creatinuria, ↓ PLT aggregation, ↓ wound healing, hepatomegaly, ↑ PT, ↑ vitamin K deficiency coagulopathy</p> <p>Propylene Glycol Toxicity:¹ ↑ osmolarity, lactic acidosis, seizures, respiratory depression</p>	<p>Rare:¹ Haemolytic anaemia</p> <p>Class ADR PIs:² Hyperglycaemia/diabetes mellitus, ketoacidosis, fat redistribution and lipid abnormalities, hyperlipidaemia, bleeding-haemophilia^{1,2,9}</p>
MONITORING (blood tests)	CBC, PT, ALT, glucose, ^{8,14} TRIG, ^{8,14} CHOL, ^{8,14} lactate	CBC, ALT, glucose, ^{8,14} TRIG, ^{8,14} CHOL, ^{8,14} urinalysis, bilirubin, BUN, Cr
DRUG INTERACTIONS	<p><u>CHECK EACH NEW DRUG Cytochrome P450 3A4 Inhibitor (RTV > IDV=NFV = APV> SQV)</u>²</p> <p>Do not use:² Cisapride, ergot alkaloids, midazolam, RIF, triazolam, Ca channel blocker bepridil, simvastatin, lovastatin, BCP</p> <p>↓ concentration of APV:² NVP, EFV, St. John's wort¹², ketoconazole, phenytoin, phenobarb, carbamazepine</p> <p>↑ concentration of:² Rifabutin (193%), sildenafil (Viagra[®]), ketoconazole</p> <p>Not recommended with:² Cisapride, amiodarone, lidocaine, warfarin, tricyclic antidepressants, quinidine, oral contraceptives (use additional methods), disulfiram, or metronidazole (propylene glycol is metabolised by alcohol and aldehyde dehydrogenase)</p> <p>OK with:² Acetaminophen, fluconazole, dimenhydrinate, azithromycin, clarithromycin, EMB, desloratadine (Aerius[®]), loratadine (Claritin[®]), fexofenadine (Allegra[®]), cetirizine (Reactine[®]), lorazepam, temazepam</p>	<p><u>MANY:</u>² <u>CHECK EACH NEW DRUG</u></p> <p>Inhibits CYP3A4 (P450) (RTV > IDV=NFV = APV > SQV)³</p> <p>Do not use: Cisapride, ergot alkaloids, triazolam, midazolam, simvastatin, lovastatin, rifampin, ATV (↑ hyperbilirubinaemia)</p> <p>↑ concentration of IDV: Ketoconazole, itraconazole, RTV, SQV, NFV</p> <p>↑ concentration: Rifabutin (use ½ dose)</p> <p>↓ concentration of IDV: St. John's wort¹², phenytoin, phenobarb, carbamazepine, grapefruit juice, NVP, EFV</p> <p>OK with:² Acetaminophen, fluconazole, dimenhydrinate, azithromycin, clarithromycin, EMB, desloratadine (Aerius[®]), loratidine (Claritin[®]), fexofenadine (Allegra[®]), cetirizine (Reactine[®]), lorazepam, temazepam, BCP</p>
MARKET STATUS ⁶⁺	50mg and 150mg capsules; 15mg/mL (240mL bottle)	200mg and 400mg capsule
DOSE IN ORGAN FAILURE	Oral solution contra-indicated in liver and renal dysfunction Liver dysfunction: 300-450mg po b.i.d (see Child-Pugh Score) ²	Mild to moderate cirrhosis: 600mg po q8h ²

PART 1 OF 3	AMPRENAVIR	INDINAVIR
CSF/PLASMA BIOAVAILABILITY HALF-LIFE	0.45-1.3% ¹³ F = unknown ² F _{liq} < F _{caps} t _{1/2} = 7.1-10.6h ²	1.7-16% ¹⁶⁻¹⁷ F = 0.65 ² t _{1/2} = 1.5-2h ²
MEALS	May take with or without food (not with high fat meal as ↓ 21% AUC ¹)	Give on empty stomach or may give with milk, juice, or light snack
SPECIAL INSTRUCTIONS	<ul style="list-style-type: none"> • As APV is a sulfonamide, potential for cross sensitivity with sulfonamide allergies¹ • Liquid in capsule is unpalatable • Do not use in children <age 4 years (vitamin E and propylene glycol toxicity), pregnant women, patients with hepatic or renal failure, and patients treated with disulfiram or metronidazole • Do not take vitamin E supplement (daily recommendation for children only 10IU/day and adults 30IU/day) • Do not use in neonates¹ (propylene glycol t_{1/2} neonate = 16.9 hours, t_{1/2} adult = 5 hours) • Oral solution does not equal capsule (bioavailability of solution 14% < capsule) • Give 1 hour before or after ddI or antacid¹ 	<ul style="list-style-type: none"> • Give 1 hour before or 2 hours after a meal (can give with light snack) • May give with a meal if given with RTV • Very unpalatable, tastes bitter • Can open capsule and mix with water • Drink lots of water • Adults should drink 48oz of water (1.5L) per day • Adults should drink so much water that they need to urinate at least once during the night • Give 1 hour before or after ddI²

Note: *Do not exceed the recommended adult dose. Some information in this chart may be at variance with the product monograph. Please consult current recommendations before using this chart.

⁺Market status does not imply approval for paediatric use.

Table 13: Protease Inhibitors (PIs) (Part 2 of 3 tables on PIs)*

PART 2 OF 3	NELFINAVIR	RITONAVIR	SAQUINAVIR SGC (SOFT-GEL CAPSULE)
SHORT FORM	NFV	RTV	SQV
TRADE NAME	Viracept® (Agouron)	Norvir® (Abbott)	sgc-Fortovase®, hgc-Invirase® (Roche)
PAEDIATRIC DOSE* Do not exceed the recommended adult dose.	Paediatric¹: Investigational (>age 6 years)¹ (8 months to 16 years):¹⁸ 50-55mg/kg/dose po b.i.d 20-30mg/kg/dose po t.i.d Routine: 30-45mg/kg/dose multiples of 50mg for powder Neonate (<age 6 weeks) PACTG 353:¹ Protocol Dose: 40mg/kg/dose po b.i.d	400mg/m ² /dose po b.i.d ¹ Range: 350-400mg/m ² /dose po b.i.d ¹ Initial: ↑ dose over 5 days USING po b.i.d: ¹ 250mg/m ² /dose x 2/7 (or ↑ dose by 100mg capsule), then 300mg/m ² /dose x 2/7, then 350mg/m ² /dose 1/7, then 400mg/m ² /dose po b.i.d Neonatal (≤12 hours postbirth) PACTG 354:¹ Protocol Dose: 350mg/m ² /dose po b.i.d x 4 weeks	Paediatric Investigational: Protocol Dose ¹ : 50mg/kg/dose SGC po q8h Protocol Dose ¹ : 33mg/kg/dose SGC po q8h plus NFV
ADOLESCENT & ADULT DOSE	1,250mg po b.i.d ^{1,2} (5 x 250mg or 2 x 625mg tablets) or 750mg po t.i.d ^{1,2} Investigational: 1, 500mg po b.i.d ¹	600mg po b.i.d ^{1,2} To ↓ nausea, ↑ dose over 5 days: ¹ 300mg po b.i.d x 2/7, 400mg po b.i.d x 2/7, 500mg po b.i.d x 1/7, then 600mg po b.i.d Pharmacokinetic booster for other PI: ² 100-400mg/day divided in 1 to 2 doses	1,200mg sgc po t.i.d ² (no initial titration is necessary) With RTV (preferred regimen): ² SQV sgc, 1,000mg + RTV, 100mg po b.i.d or SQV sgc, 400mg + RTV, 400mg po b.i.d
CANADIAN AVAILABLE FORMS⁶ & STORAGE	250mg and 625mg tablets (not scored - may cut in half) ²¹ room temperature, Rx vial 200mg/5mL level scoop 50mg in 1g powder 144g, room temp, original bottle	100mg soft-elastic capsule (120/bottle). Refrigerate until dispensed, then 30 days at room temperature, original bottle 80mg/mL peppermint/caramel-flavoured (240mL), room temperature, original bottle Contains saccharin and possibly lecithin ⁵ (peanut allergy???) and coconut oil ⁵	200mg sgc (preferred product) refrigerate until dispensed, then 3 months room temperature, Rx vial 200mg hgc (hard-gel capsule) Rx vial, room temperature
MAIN PRECAUTION	Diarrhoea	Drug interactions, nausea and vomiting	Drug interactions
TOXICITY	Most Common: ^{1,2} Diarrhoea (20%)	More Common: Nausea, vomiting, diarrhoea, headache, abdominal pain, anorexia	More Common: ¹ Diarrhoea, abdominal discomfort, headache, nausea, paresthaesias, skin

PART 2 OF 3	NELFINAVIR	RITONAVIR	SAQUINAVIR SGC (SOFT-GEL CAPSULE)
	<p>Less Common:¹ Asthaenia, abdominal pain, rash, and exacerbation of chronic liver disease</p> <p>ADRs for PI Class:²: Hyperglycaemia/diabetes mellitus, fat redistribution and lipid abnormalities, hyperlipidaemia, bleeding-haemophilia^{1,2,9}</p>	<p>Less Common:¹ Paresthaesias (circumoral/extremities), ↑ LFTs, taste perversion²</p> <p>Rare:¹ Pancreatitis, ↑ CHOL, ↑ TRIG, hepatitis</p> <p>ADRs for PI Class:² Hyperglycaemia/diabetes mellitus, ketoacidosis, fat redistribution and lipid abnormalities, hyperlipidaemia, bleeding-haemophilia^{1,2,9}</p>	<p>rash</p> <p>Less Common:¹ ↑ chronic liver disease, ↑ LFTs²</p> <p>ADRs for PI Class:² Hyperglycaemia/diabetes mellitus, ketoacidosis, fat redistribution and lipid abnormalities, hyperlipidaemia, bleeding-haemophilia^{1,2,9}</p>
MONITORING (blood tests)	CBC, ALT, glucose, ^{8,14} TRIG, ^{8,14} CHOL ^{8,14}	ALT, amylase, glucose, ^{8,14} TRIG, ^{8,14} CHOL ^{8,14}	CBC, ALT, glucose, ^{8,14} TRIG, ^{8,14} CHOL ^{8,14}
DRUG INTERACTIONS	<p><u>MANY:</u>² <u>CHECK EACH NEW DRUG</u></p> <p>Inhibits CYP3A4 (P450) (RTV > IDV = NFV = APV > SQV)³</p> <p>Do not use with:² Cisapride, ergot alkaloids, simvastatin, lovastatin, rifampin, neuroleptics (pimozide - Orap[®]), midazolam, triazolam, St. John's wort¹², BCP (use additional methods)</p> <p>Adjust dose:¹ SQV, RTV, IDV, DLV, NVP, voriconazole, rifabutin (½ dose rifabutin)</p> <p>↓ concentration of NFV: Phenytoin, phenobarb, carbamazepine</p> <p>OK with:² Acetaminophen, fluconazole, ketoconazole, dimenhydrinate, azithromycin, clarithromycin, EMB, desloratadine (Aerius[®]), loratadine (Claritin[®]), fexofenadine (Allegra[®]), cetirizine (Reactine[®]), lorazepam, temazepam</p>	<p><u>MANY:</u>² <u>CHECK EACH NEW DRUG</u></p> <p>Inhibits CYP3A > CYP2D6 > CYP2C9 > CYPC19 (RTV > IDV = NFV = APV > SQV)³</p> <p>Do not use with:^{1,2,10} Cisapride, rifabutin (↑ uveitis, arthralgia, leukopaenia), RIF (↑ liver toxicity), meperidine, pimozide, desipramine, loratadine, fluoxetine, simvastatin, lovastatin, midazolam, triazolam, alprazolam, clorazepate, diazepam, estazolam, zolpidem, clozapine, bupropion, ergot alkaloids, Ca channel blocker bepridil, amiodarone, BCP (↓ 40% AUC ethinyl estradiol)⁵, flecanide, encainide, propafenone, quinidine, St. John's wort (↓ RTV)¹², grapefruit juice, voriconazole, fluticasone</p> <p>Use with caution:^{1,2,10} Erythromycin, digoxin, itraconazole, ketoconazole, SQV, IDV, NFV, warfarin, metronidazole, dexamethasone, carbamazepine, phenobarb, phenytoin, ibuprofen (Advil[®]) [predicted ↑ AUC ibuprofen (RTV inhibits CYP2C9) or ↓ AUC (RTV induces glucuronoyl transferase)] dextromethorphan (DM) (metabolised by CYP2D6)</p> <p>OK with:² Acetaminophen, fluconazole, dimenhydrinate (use ¼ dose), azithromycin,</p>	<p><u>MANY:</u>² <u>CHECK EACH NEW DRUG</u></p> <p>Inhibits CYP 3A4 (RTV > IDV = NFV = APV > SQV)³</p> <p>Do not use with:² Simvastatin, lovastatin, RIF, rifabutin, cisapride, midazolam, triazolam, ergot alkaloids, St. John's wort,¹² garlic supplements</p> <p>↑ concentration of SQV: Cimetidine, erythromycin, RTV, IDV, NFV, ATV, DLV, ketoconazole, grapefruit juice</p> <p>↓ concentration of SQV: NVP, phenytoin, phenobarb, carbamazepine, dexamethasone,</p> <p>↑ concentration: Ca channel blockers, clindamycin, dapsone, quinidine</p> <p>OK with:² Acetaminophen, fluconazole, dimenhydrinate, azithromycin, clarithromycin, EMB, desloratadine (Aerius[®]), loratadine (Claritin[®]), fexofenadine, (Allegra[®]), cetirizine (Reactine[®]), lorazepam, temazepam</p>

PART 2 OF 3	NELFINAVIR	RITONAVIR	SAQUINAVIR SGC (SOFT-GEL CAPSULE)
		clarithromycin (↓ dose in renal dysfunction), EMB, desloratadine (Aerius [®]), loratadine (Claritin [®]), fexofenadine (Allegra [®]), cetirizine (Reactine [®]), lorazepam, temazepam	
MARKET STATUS ⁶⁺	Marketed	Marketed	Soft-gel capsule and hard-gel capsule marketed
DOSE IN ORGAN FAILURE	Caution: Decrease dose with hepatic dysfunction	Caution: Decrease dose with liver dysfunction	Caution: Decrease dose with liver dysfunction
CSF/PLASMA	Brain penetration in rats ¹³	Negligible (< 0.05mg/L ¹³)	Negligible ¹³
KINETICS BIOAVAILABILITY HALF-LIFE	$Cl_{paediatric} 2-3x > Cl_{adult}$ $F = 0.2-0.8^2$ $t_{1/2} = 3.5-5h^2$	Protein binding = 98-99% $t_{1/2} = 3-5h^2$	Protein binding = 98% $F_{hgc} = 0.04^2$ $t_{1/2} = 1-2h^2$
MEALS	Give with meal	Take with food	Take with food
SPECIAL INSTRUCTIONS	<ul style="list-style-type: none"> • Bitter if mixed with acidic food or juice • 250mg and 625mg tablets dissolve readily in water²¹ (½ tablet in 2mL, 1-2 tablets in 5mL minimum); can be added to milk or chocolate milk • 250mg and 625mg tablets can be crushed and added to pudding • Measure out powder and mix with water, milk, formula, pudding, ice cream, chocolate milk • Mix well as drug will settle • Powder has gritty and thick texture (G-tube blockage with powder or dissolved tablet) • Do not add water to bottle of oral powder—use special scoop • Give 2 hours before or 1 hour after ddi¹ • Tablet or powder may be mixed with food or liquid up to 6 hours before dose is taken¹ 	<ul style="list-style-type: none"> • May develop resistance if only a few doses are missed • Liquid is unpalatable, bad aftertaste:¹ <ol style="list-style-type: none"> 1) Dull taste buds: give after Popsicle or frozen juice 2) Give with fat: ice cream, high-fat dairy product 3) Coat mouth: give after grape jelly, maple syrup, or peanut butter on toast 4) Mix with: formula, milk, chocolate milk, ice cream, pudding, maple syrup, Tang[®], Ensure[®] 5) Give strong flavour after dose: maple syrup, cheese, strong-flavoured chewing gum • Flush G-tube with milk or enteral feed • Give 2 hours before or after ddi² 	<ul style="list-style-type: none"> • Give ≤2 hours after full meal or large snack to increase absorption • Unpalatable (very bitter) • hgc-Invirase[®] contains powder in capsule that can be opened and sprinkled on food or water, but has unpalatable taste • Give with grapefruit if not on RTV • Wear sunscreen (photosensitivity <2% patients) • sgc-Fortovase[®] contains liquid or gel in capsule

Note: *Do not exceed the recommended adult dose. Some information in this chart may be at variance with the product monograph. Please consult current recommendations before using this chart.

[†]Market status does not imply approval for paediatric use.

Table 14: Protease Inhibitor (PIs)* Combinations (Part 3 of 3 tables on PIs)

PART 3 OF 3	LOPINAVIR PLUS RITONAVIR
SHORT FORM	ABT-378/r; LPV/r; LPV/RTV
TRADE NAME	Kaletra® (ABB)
PAEDIATRIC DOSE* Do not exceed the recommended adult dose.	<p>Age 6 months to 12 years: 230/57.5mg/m²/dose po b.i.d.¹</p> <p>With concomitant therapy with EFV, NVP, or reduced LPV susceptibility:¹</p> <p>Age 6 months to 12 years: 300/75mg/m²/dose po b.i.d</p>
ADOLESCENT & ADULT DOSE	<p>400mg/100mg po b.i.d.^{1,2} (3 capsules or 5mL po b.i.d)</p> <p>With concomitant therapy with EFV or NVP:^{1,2} Maximum: 533/133mg po b.i.d (4 capsules or 6.5mL po b.i.d)^{1,11}</p>
CANADIAN AVAILABLE FORMS ⁶ & STORAGE	<p>133.3mg LPV/33.3mg RTV orange soft gelatin capsules (180/bottle)</p> <ul style="list-style-type: none"> • Capsule contains propylene glycol¹¹ and possibly lecithin⁵ (peanut allergy???) and coconut oil⁵ • Refrigerate until dispensed, then 6 weeks at room temperature,¹¹ original bottle <p>Oral solution 80mg LPV/20mg RTV/mL (160mL/bottle) contains: Alcohol 42.4% v/v¹¹(alcohol sg 0.789), cotton candy-flavour, sugar, propylene glycol, and saccharin; refrigerate until dispensed, then 6 weeks at room temperature¹¹; original BTL</p>
MAIN PRECAUTION	Rash, drug interactions
TOXICITY	<p>More Common:¹ Diarrhoea, headache, asthenia, nausea and vomiting, rash</p> <p>Rare: Pancreatitis, hepatitis</p> <p>Class ADR PIs:² Hyperglycaemia/diabetes mellitus, ketoacidosis, fat redistribution and lipid abnormalities, hyperlipidaemia, bleeding-haemophilia^{1,2,9}</p> <p style="text-align: center;">SEE ritonavir</p>
MONITORING (blood tests)	CBC, PT, ALT, glucose, ^{8,14} TRIG, ^{8,14} CHOL, ^{8,14} bilirubin, amylase

PART 3 OF 3	LOPINAVIR PLUS RITONAVIR
DRUG INTERACTIONS	<p>MANY: CHECK EACH NEW DRUG: SEE ritonavir (RTV > IDV = NFV = APV > SQV)³ LPV is metabolised by CYP3A (RTV ↑ LPV concentration) RTV concentration <7% of levels compared to RTV 600mg po b.i.d¹¹</p> <p>Do not use with: flecainide, propafenone, simvastatin, lovastatin, RIF, cisapride, proton pump inhibitors, neuroleptics (pimozide - Orap[®]), midazolam, triazolam, ergot alkaloids, St. John's wort¹²</p> <p>↓ concentration of LPV:¹ EPV, NVP, carbamazepine, phenytoin, phenobarbital, dexamethasone, inhaled or intranasal fluticasone (Cushing's syndrome and adrenal suppression)¹¹</p> <p>↓ concentration of:¹ BCP (use additional methods), atovaquone</p> <p>↑ concentration of:¹ rifabutin (75%), sildenafil (Viagara[®]), amiodarone, lidocaine, cyclosporine, tacrolimus, rapamycin, calcium channel blockers, ketoconazole, itraconazole</p> <ul style="list-style-type: none"> • May need to ↑ dose of ABC, AZT (↑ glucuronidation)¹¹ • Decrease dose with clarithromycin when CrCl <60mL/min¹¹ <p>OK with:² acetaminophen, Septra[®], dapsone, azithromycin, EMB, dimenhydrinate, desloratadine (Aerius[®]), loratadine (Claritin[®]), fexofenadine (Allegra[®]), cetirizine (Reactine[®]), lorazepam, temazepam, fluconazole, d4T, 3TC¹¹</p>
MARKET STATUS⁶⁺	Marketed in Canada
DOSE IN ORGAN FAILURE	Caution: Decrease dose with liver dysfunction
CSF/PLASMA BIOAVAILABILITY HALF-LIFE	t _{1/2} = 5-6h ²
MEALS	Take with food
SPECIAL INSTRUCTIONS	<ul style="list-style-type: none"> • Capsule contains propylene glycol¹¹ and possibly lecithin⁵ (peanut allergy???) and coconut oil⁵ • Oral solution contains alcohol 42.4% v/v¹¹ (alcohol sg 0.789), cotton candy-flavouring, sugar, propylene glycol, and saccharin • Refrigerate oral solution and capsules until dispensed, then 6 weeks at room temperature¹¹ in the original bottle • Give with high-fat meal to enhance oral absorption • Calculate dose of alcohol with liquid formulation • See ritonavir special instructions • Take ddI 1 hour before or 2 hours after Kaletra[®]

Note:

*Do not exceed the recommended adult dose. Some information in this chart may be at variance with the product monograph. Please consult current recommendations before using this chart.

[†]Market status does not imply approval for paediatric use. Fosamprenavir f-APV(Telzir[®] Canada, Lexiva[®] USA GSK) 700mg tablet and Atazanavir (ATV) (Reyataz[®] BMS) 150 and 200mg capsules marketed in Canada but do not have paediatric dosing guidelines yet.

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Table 15: Fusion Inhibitors*

PART 1 OF 1	ENFUVIRTIDE
SHORT FORM	T-20
TRADE NAME	Fuzeon [®] (Roche)
PAEDIATRIC DOSE* Do not exceed the recommended adult dose.	Paediatric (age 6-16 years): ¹ 2mg/kg/dose SC b.i.d to maximum of 90 (1mL) SC b.i.d
ADOLESCENT & ADULT DOSE	90mg (1mL) SC b.i.d
CANADIAN AVAILABLE FORMS⁴ & STORAGE	90mg/mL: lyophilised powder for injection 108mg reconstituted with 1.1ml of sterile water for injection. Store powder at room temperature (60/box).
MAIN PRECAUTION	Hypersensitivity reaction
TOXICITY	Most Common: ^{1,2} 98% of patients experience mild to moderate local injection site reactions including pain, discomfort, induration, erythema (usually lasts 2-3 days), nodules, cysts, pruritis, and ecchymosis. Less Common: ¹ Eosinophilia (11.2% vs. controls 2.4%), ³ bacterial pneumonia (unclear association) Rare (<1%): ¹ Hypersensitivity reactions (fever, nausea, vomiting, chills, rigors, hypotension, ↑ LFTs); immune-mediated reactions (primary immune complex reaction, respiratory distress, glomerulonephritis, Guillain-Barré syndrome). Do not restart therapy.
MONITORING (blood tests)	CBC, ALT, Cr
DRUG INTERACTIONS	None reported ¹
MARKET STATUS⁴⁺	Marketed
DOSE IN ORGAN FAILURE	No adjustment in renal failure required ²
CSF/PLASMA BIOAVAILABILITY HALF-LIFE	t _{1/2} = 3.8h ²

PART 1 OF 1	ENFUVIRTIDE
MEALS	
SPECIAL INSTRUCTIONS	<p>Reconstitution: Slowly inject 1.1mL of sterile water for injection into the lyophilised powder, letting the drops gently slide down the side of the vial. Gently tap vial for 10 seconds, then slowly roll the vial in the palm of your hands to dissolve the powder. DO NOT SHAKE. May take up to 45 minutes to completely go into solution. (Do not shake or add water quickly as protein powder will foam and take up to 24 hours to settle.) Reconstituted solution stable for 24 hours when refrigerated.</p> <p>Administration using EMLA[®] (topical anaesthetic): Prepare both doses in the evening so the morning dose is ready to use. Let the prepared dose warm up to room temperature before injecting. If required, apply EMLA[®] to injection site (takes 1 hour for full pain control). Wipe off EMLA[®] (topical anaesthetic) and rub injection site with ice for several minutes. Use sterile technique, inject the drug SC at a 30°-40° angle into upper arm, anterior thigh, or abdomen. Rotate injection sites.</p> <p>If signs and symptoms of a hypersensitivity reaction occur, discontinue treatment and immediately seek medical attention. Do not restart following a suspected hypersensitivity reaction.</p> <p>Soreness at the injection site is common but rarely the reason for the patient to discontinue the drug: redness, pain, lymph node swelling, mild itching, bruising, swelling, and tenderness may occur.</p>

Note:

*Do not exceed the recommended adult dose. Some information in this chart may be at variance with the product monograph. Please consult current recommendations before using this chart.

+Market status does not imply approval for paediatric use.

**Globally, dose use at \geq age 3 months.

References:

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APPENDIX IX-C: CLASSIFICATION OF PAEDIATRIC HIV/AIDS

HIV/AIDS in infants and children age thirteen years or younger may be classified using WHO criteria (*Table 16*). Alternately, the revised CDC criteria may be used, which offers more specific clinical diagnostic Categories of A, B, and C for mild, moderate, and severe disease, respectively (*Table 17*), as well as immunological criteria of Class 1, 2, and 3 for mild, moderate, and severe immunosuppression, respectively (*Table 18*).

Table 16: WHO Staging System for HIV Infection and Disease in Children

CLINICAL STAGE I <ul style="list-style-type: none">• Asymptomatic• Generalised lymphadenopathy
CLINICAL STAGE II <ul style="list-style-type: none">• Unexplained chronic diarrhoea• Severe persistent or recurrent candidiasis outside the neonatal period• Weight loss or failure to thrive• Persistent fever• Recurrent severe bacterial infections
CLINICAL STAGE III <ul style="list-style-type: none">• AIDS-defining opportunistic infections (OIs)• Severe failure to thrive (wasting in the absence of known aetiology)*• Progressive encephalopathy• Malignancy• Recurrent septicaemia or meningitis

*Persistent weight loss of >10% of baseline or <5th percentile on weight-for-height chart on 2 consecutive measurements >1 month apart in the absence of another aetiology or concurrent illness.

Table 17: 1994 CDC Revised Human Immunodeficiency Virus Paediatric Classification System: Clinical Categories

CATEGORY N: NOT SYMPTOMATIC

Children who have no signs or symptoms considered to be the result of HIV infection or who have only one of the conditions listed in Category A.

CATEGORY A: MILDLY SYMPTOMATIC

Children with **2** or more of the following conditions but none of the conditions listed in Categories B and C:

- Lymphadenopathy (>0.5cm at >2 sites; bilateral = 1 site)
- Hepatomegaly
- Splenomegaly
- Dermatitis
- Parotitis
- Recurrent or persistent upper respiratory infection, sinusitis, or otitis media

CATEGORY B: MODERATELY SYMPTOMATIC

Children who have symptomatic conditions, other than those listed for Category A or Category C, which are attributed to HIV infection. Examples of conditions in clinical Category B include, but are not limited to, the following:

- Anaemia (<8gm/dL), neutropaenia (<1,000/mm³), or thrombocytopaenia (<100,000/mm³) persisting >30 days
- Bacterial meningitis, pneumonia, or sepsis (single episode)
- Candidiasis, oropharyngeal (e.g. thrush) persisting for >2 months in children age >6 months
- Cardiomyopathy
- Cytomegalovirus (CMV) infection with onset before age 1 month
- Diarrhoea, recurrent or chronic
- Hepatitis
- Herpes simplex virus (HSV) stomatitis, recurrent (e.g. >2 episodes within 1 year)
- HSV bronchitis, pneumonitis, or oesophagitis with onset before age 1 month
- Herpes zoster (e.g. shingles) involving at least 2 distinct episodes or more than 1 dermatome
- Leiomyosarcoma
- Lymphoid interstitial pneumonia (LIP) or pulmonary lymphoid hyperplasia complex
- Nephropathy
- Nocardiosis
- Fever lasting >1 month
- Toxoplasmosis with onset before age 1 month
- Varicella, disseminated (e.g. complicated chickenpox)

CATEGORY C: SEVERELY SYMPTOMATIC

- Serious bacterial infections, multiple or recurrent (e.g. any combination of at least 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 indwelling 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
- CMV disease with onset of symptoms at age >1 month (at a site other than liver, spleen, or lymph nodes)
- Encephalopathy (at least 1 of the following progressive findings present for at least 2 months in the absence of a concurrent illness other than HIV infection that could explain the findings): a) failure to attain or loss of developmental milestones or loss of intellectual ability, verified by standard developmental scale or neuropsychological tests; b) impaired brain growth or acquired microcephaly demonstrated by head circumference measurements or brain atrophy demonstrated by CT or MRI (serial imaging is required for children age <2 years); c) acquired symmetric motor deficit manifested by 2 or more of the following: paresis, pathologic reflexes, ataxia, or gait disturbance; d) HSV infection causing a mucocutaneous ulcer that persists for >1 month; or e) bronchitis, pneumonitis, or oesophagitis for any duration affecting a child age >1 month
- Histoplasmosis, disseminated (at a site other than or in addition to lungs or cervical or hilar lymph nodes)
- Kaposi's sarcoma (KS)
- Lymphoma, primary, in brain
- Lymphoma, small, noncleaved cell (Burkitt's), or immunoblastic or large cell lymphoma of B-cell or unknown immunologic phenotype
- *Mycobacterium tuberculosis*, disseminated or extrapulmonary *Mycobacterium*, other species or unidentified species, disseminated (at a site other than or in addition to lungs, skin, or cervical or hilar lymph nodes)
- *Mycobacterium avium* complex or *Mycobacterium kansasii*, disseminated (at site other than or in addition to lungs, skin, or cervical or hilar lymph nodes)
- *Pneumocystis carinii* pneumonia (PCP)
- Progressive multifocal leukoencephalopathy (PML)
- *Salmonella* (nontyphoid) septicaemia, recurrent
- Toxoplasmosis of the brain with onset at age >1 month
- Wasting syndrome in the absence of a concurrent illness other than HIV infection that could explain the following findings: a) persistent weight loss >10% of baseline; OR b) downward crossing of at least 2 of the following percentile lines on the weight-for-age chart (e.g. 95th, 75th, 50th, 25th, 5th) in a child age ≥1 year; OR c) <5th percentile on weight-for-height chart on 2 consecutive measurements, ≥30 days apart PLUS a) chronic diarrhoea (e.g. at least 2 loose stools/day for >30 days); OR b) documented fever (for ≥30 days, intermittent or constant)

Table 18: Human Immunodeficiency Virus: Paediatric Immune Category Classification System Based on Age-Specific CD4+ T Cell Count and Percentage

IMMUNE CATEGORY/CLASS	DEGREE OF IMMUNE SUPPRESSION	AGE <12 MONTHS	AGE 1-5 YEARS	AGE 6-12 YEARS
1	None, or mild	1,500 and $\geq 25\%$	$\geq 1,000$ and $\geq 25\%$	≥ 500 and $\geq 25\%$
2	Moderate	750-1,499 or 15-24%	500-999 or 15-24%	200-499 or 15-24%
3	Severe	<750 or < 15%	<500 or <15%	<200 or <15%

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