Guidelines for the Use of Antiretroviral Agents in Pediatric HIV-Infection

Tables and Figures

February 23, 2009 release

The in-text and appendix tables from the February 23, 2009, release of the **Guidelines for the Use of Antiretroviral Agents in Pediatric HIV-Infection** have been compiled in this document to facilitate downloading. Each table is identical in numbering and content to those found in the guidelines document. References within these tables may be found in the appropriate section of the guidelines document, when applicable.

Table 1: 1994 Revised Human Immunodeficiency Virus Pediatric Classification System: Clinical Categories* (Updated February 28, 2008)

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 (≥0.5 cm at more than two sites; bilateral = one 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, that are attributed to HIV infection. Examples of conditions in clinical category B include, but are not limited to, the following:

- Anemia (<8 gm/dL), neutropenia (<1,000 cells/mm^3), or thrombocytopenia (<100,000 cells/mm^3) persisting ≥30 days
- Bacterial meningitis, pneumonia, or sepsis (single episode)
- Candidiasis, oropharyngeal (i.e., thrush) persisting for >2 months in children aged >6 months
- Cardiomyopathy
- Cytomegalovirus infection with onset before age 1 month
- Diarrhea, recurrent or chronic
- Hepatitis
- Herpes simplex virus (HSV) stomatitis, recurrent (i.e., more than two episodes within 1 year)
- HSV bronchitis, pneumonitis, or esophagitis with onset before age 1 month
- Herpes zoster (i.e., shingles) involving at least two distinct episodes or more than one 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 (i.e., complicated chickenpox)

Table 1: 1994 Revised Human Immunodeficiency Virus Pediatric Classification System: Clinical Categories* (cont'd)
(Updated February 28, 2008)

Category C: Severely Symptomatic

Children who have any condition listed in the 1987 surveillance case definition for acquired immunodeficiency syndrome (below), with the exception of LIP (which is a category B condition)

- Serious bacterial infections, multiple or recurrent (i.e., any combination of at least two culture-confirmed infections within a 2-year period), of the following types: septicemia, 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, esophageal 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 diarrhea persisting >1 month
- Cytomegalovirus disease with onset of symptoms at age >1 month (at a site other than liver, spleen, or lymph nodes)
- Encephalopathy (at least one 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 computerized tomography or magnetic resonance imaging (serial imaging is required for children <2 years of age); c) acquired symmetric motor deficit manifested by two or more of the following: paresis, pathologic reflexes, ataxia, or gait disturbance
- Herpes simplex virus infection causing a mucocutaneous ulcer that persists for >1 month; or bronchitis, pneumonitis, or esophagitis for any duration affecting a child >1 month of age
- Histoplasmosis, disseminated (at a site other than or in addition to lungs or cervical or hilar lymph nodes)
- Kaposi's sarcoma
- Lymphoma, primary, in brain
- Lymphoma, small, noncleaved cell (Burkitt'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 jiroveci pneumonia
- Progressive multifocal leukoencephalopathy
- Salmonella (nontyphoid) septicemia, recurrent
- Toxoplasmosis of the brain with onset at >1 month of age
- Wasting syndrome in the absence of a concurrent illness other than HIV infection that could explain the following findings: a) persistent weight loss >10% of baseline; OR b) downward crossing of at

* Centers for Disease Control and Prevention. 1994 Revised classification system for human immunodeficiency virus infection in children less than 13 years of age. *MMWR*, 1994. 43 (No. RR-12): p. 1–10.

days), OR 2) documented fever (for ≥30 days, intermittent or constant)

Table 2: Indications for Initiation of Antiretroviral Therapy in Children Infected with Human Immunodeficiency Virus (HIV) (Updated February 28, 2008)

This table provides general guidance rather than absolute recommendations for an individual patient. Factors to be considered in decisions about initiation of therapy include the risk of disease progression as determined by CD4 percentage or count and plasma HIV RNA copy number; the potential benefits and risks of therapy; and the ability of the caregiver to adhere to administration of the therapeutic regimen. Issues associated with adherence should be fully assessed, discussed, and addressed with the child, if age appropriate, and caregiver before the decision to initiate therapy is made.

Age	Criteria	Recommendation
<12 months	• Regardless of clinical symptoms, immune status, or viral load	*Treat*
1–<5 years	• AIDS or significant HIV-related symptoms [1]	*Treat*
	• CD4 <25%, regardless of symptoms or HIV RNA level [2]	*Treat*
	• Asymptomatic or mild symptoms [3] *and* o CD4 ≥25% *and* o HIV RNA ≥100,000 copies/mL	*Consider*
	• Asymptomatic or mild symptoms [3] *and* o CD4 ≥25% *and* o HIV RNA <100,000 copies/mL	*Defer* [4]
≥5 years	• AIDS or significant HIV-related symptoms [1]	*Treat*
	• CD4 <350 cells/mm^3 [5]	*Treat*
	• Asymptomatic or mild symptoms [3] *and* o CD4 ≥350 cells/mm^3 *and* o HIV RNA ≥100,000 copies/mL	*Consider*
	• Asymptomatic or mild symptoms [3] *and* o CD4 ≥350 cells/mm^3 *and* o HIV RNA <100,000 copies/mL	*Defer* [4]

[1] CDC Clinical Category C and B (except for the following category B conditions: single episode of serious bacterial infection or lymphoid interstitial pneumonitis)

[2] The data supporting this recommendation are stronger for those with CD4 percentage <20% than for those with CD4 percentage of 20%–24%.

[3] CDC Clinical Category A or N or the following category B conditions: single episode of serious bacterial infection or lymphoid interstitial pneumonitis

[4] Clinical and laboratory data should be re-evaluated every 3 to 4 months.

[5] The data supporting this recommendation are stronger for those with CD4 count <200 than for those with CD4 counts of 200–350 cells/mm^3.

Table 3: Recommended Antiretroviral Regimens for Initial Therapy for Human Immunodeficiency Virus (HIV) Infection in Children
(Updated February 23, 2009)

A combination antiretroviral regimen in treatment-naïve children generally contains 1 NNRTI plus a 2-NRTI backbone or 1 PI plus a 2-NRTI backbone. A 3-NRTI regimen consisting of zidovudine, abacavir, and lamivudine is recommended only if a PI- or NNRTI-regimen can't be used. Regimens should be individualized based on advantages and disadvantages of each combination (see **Tables 6, 7, 8**).

Non-Nucleoside Reverse Transcriptase Inhibitor-Based Regimens	
Preferred Regimen:	Children ≥3 years old: Two NRTIs ***plus*** efavirenz [1]
	Children <3 years old or who can't swallow capsules: Two NRTIs ***plus*** nevirapine[1]
Alternative:	Two NRTIs ***plus*** nevirapine[1] (children ≥3 years old)
Protease Inhibitor-Based Regimens	
Preferred Regimen:	Two NRTIs ***plus*** lopinavir/ritonavir
Alternative (listed alphabetically):	Two NRTIs ***plus*** atazanavir ***plus*** low dose ritonavir (children ≥6 years old)
	Two NRTIs ***plus*** fosamprenavir ***plus*** low dose ritonavir (children ≥6 years old)
	Two NRTIs ***plus*** nelfinavir (children ≥2 years old)
Use in Special Circumstances	
	Two NRTIs ***plus*** atazanavir unboosted (for treatment-naïve adolescents ≥13 years of age and >39 kg)
	Two NRTIs ***plus*** fosamprenavir unboosted (children ≥2 years old)
	Zidovudine ***plus*** lamivudine ***plus*** abacavir
2-NRTI Backbone Options (for use in combination with additional drugs) (alphabetical ordering)	
Preferred	Abacavir ***plus*** (lamivudine ***or*** emtricitabine)
	Didanosine ***plus*** emtricitabine
	Tenofovir ***plus*** (lamivudine ***or*** emtricitabine) (for Tanner Stage 4 or post-pubertal adolescents only)
	Zidovudine ***plus*** (lamivudine ***or*** emtricitabine)
Alternative	Abacavir ***plus*** zidovudine
	Zidovudine ***plus*** didanosine
Use in Special Circumstances	Stavudine ***plus*** (lamivudine ***or*** emtricitabine)

Table 3: Recommended Antiretroviral Regimens for Initial Therapy for Human Immunodeficiency Virus (HIV) Infection in Children (cont'd)
(Updated February 23, 2009)

Insufficient Data to Recommend for Initial Therapy
Low-dose ritonavir-boosted PI regimens, with exceptions of lopinavir/ritonavir (any age), atazanavir/ritonavir in children ≥6 years old, and fosamprenavir/ritonavir in children ≥6 years old[2]
Dual (full-dose) PI regimens
NRTI ***plus*** NNRTI ***plus*** PI
Tenofovir-containing regimens in children in Tanner stage 1–3
Unboosted atazanavir-containing regimens in children <13 years of age and/or <39 kg
Tipranavir- or darunavir-containing regimens
Etravirine-containing regimens
Enfuvirtide (T-20)-containing regimens
Maraviroc-containing regimens
Raltegravir-containing regimens

[1] Efavirenz is currently available only in capsule form and should only be used in children ≥3 years old with weight ≥10 kg; nevirapine would be the preferred NNRTI for children age <3 years old or who require a liquid formulation. Unless adequate contraception can be assured, efavirenz-based therapy is not recommended for adolescent females who are sexually active and may become pregnant.

[2] With the exception of lopinavir/ritonavir, atazanavir/ritonavir in children ≥6 years old, and fosamprenavir in combination with low-dose ritonavir in children ≥6 years old, use of other boosted PIs as a component of initial therapy is not recommended, although such regimens have utility as secondary treatment regimens for children who have failed initial therapy.

NRTI: Nucleoside analogue reverse transcriptase inhibitor; NNRTI: Non-nucleoside analogue reverse transcriptase inhibitor; PI: Protease Inhibitor

Table 4: Antiretroviral Regimens or Components that Should Not Be Offered for Treatment of Human Immunodeficiency Virus (HIV) Infection in Children (Updated July 29, 2008)

	Rationale	Exceptions
Antiretroviral regimens not recommended		
Monotherapy	• Rapid development of resistance • Inferior antiviral activity compared to combination with ≥3 antiretroviral drugs	• HIV-exposed infants (with negative viral testing) during 6-week period of prophylaxis to prevent perinatal transmission
Two NRTIs alone	• Rapid development of resistance • Inferior antiviral activity compared to combination with ≥3 antiretroviral drugs	• Not recommended for initial therapy; for patients currently on this treatment, some clinicians may opt to continue if virologic goals are achieved
Tenofovir ***plus*** ABC ***plus*** 3TC ***or*** FTC as a triple NRTI regimen	• High rate of early viral failure when this triple NRTI regimen used as initial therapy in treatment-naive adults	• No exception
Tenofovir ***plus*** ddI ***plus*** 3TC ***or*** FTC as a triple NRTI regimen	• High rate of early viral failure when this triple NRTI regimen used as initial therapy in treatment-naive adults	• No exception
Antiretroviral components not recommended as part of an antiretroviral regimen		
Atazanavir ***plus*** indinavir	• Potential additive hyperbilirubinemia	• No exception
Dual NRTI combinations:		
• 3TC ***plus*** FTC	• Similar resistance profile and no additive benefit	• No exception
• d4T ***plus*** ZDV	• Antagonistic effect on HIV	• No exception
• d4T ***plus*** ddI	• Significant toxicities including lipoatrophy, peripheral neuropathy, hyperlactatemia including symptomatic and life-threatening lactic acidosis, hepatic steatosis, and pancreatitis	• May be considered for use in antiretroviral-experienced children who require therapy change
Efavirenz in first trimester of pregnancy or sexually active adolescent girls of childbearing potential	• Potential for teratogenicity	• When no other antiretroviral option is available and potential benefits outweigh risks
Nevirapine initiation in adolescent girls with CD4 >250 cells/mm^3 or adolescent boys with CD4 >400 cells/mm^3	• Increased incidence of symptomatic (including serious and potentially fatal) hepatic events in these patient groups	• Only if benefit clearly outweighs the risk
Unboosted saquinavir	• Poor oral bioavailablity • Inferior virologic activity compared to other protease inhibitors	• No exception

NRTI: Nucleoside analogue reverse transcriptase inhibitor; NNRTI: Non-nucleoside analogue reverse transcriptase inhibitor
ABC: Abacavir; ddI: Didanosine; FTC: Emtricitabine; 3TC: Lamivudine; d4T: Stavudine; ZDV: Zidovudine

Table 5: Advantages and Disadvantages of Different Nucleoside or Nucleotide Analogue Reverse Transcriptase Inhibitor (NRTI, NtRTI) Backbone Combinations for Use in Highly Active Antiretroviral Combination Regimens for Initial Therapy in Children (Updated February 28, 2008)

	Advantages	Disadvantages
Preferred Combinations		
ABC ***plus*** 3TC ***or*** FTC	• Palatable liquid formulations • Can give with food • ABC and 3TC are coformulated as a single pill for older/larger patients	• Potential for ABC hypersensitivity reaction; consider HLA-B*5701 screening prior to initiation of ABC treatment
ddI ***plus*** FTC	• Delayed-release capsules of ddI may allow once-daily dosing in older children able to swallow pills and who can receive adult dosing along with once-daily FTC • FTC available as a palatable liquid formulation administered once daily	• Food effect (ddI is recommended to be taken 1 hour before or 2 hours after food) – some experts give ddI without regard to food in infants or when compliance is an issue (but can be coadministered with FTC) • Limited pediatric experience using delayed-release capsules in younger children • Pancreatitis, neurotoxicity with ddI
ZDV ***plus*** 3TC ***or*** FTC	• Extensive pediatric experience • Coformulated as single pill for older/larger patients • Palatable liquid formulations • Can give with food • FTC available as a palatable liquid formulation administered once daily	• Bone marrow suppression with ZDV
Tenofovir ***plus*** 3TC ***or*** FTC for Tanner stage 4 or postpubertal adolescents only	• Resistance slow to develop • Once-daily dosing for tenofovir (adults) • Less mitochondrial toxicity than other NRTIs • Can give with food • Bone toxicity may be less in postpubertal children • Tenofovir and FTC are coformulated as single pill for older/larger patients	• No pediatric formulation of tenofovir • Limited pediatric experience • Potential bone and renal toxicity • Numerous drug-drug interactions with other antiretroviral agents including ddI, LPV/RTV, ATV, and TPV, complicating appropriate dosing
Alternate Combinations		
ABC ***plus*** ZDV	• Palatable liquid formulations • Can give with food	• Potential for ABC hypersensitivity reaction; consider HLA-B*5701 screening prior to initiation of ABC treatment • Bone marrow suppression with ZDV
ZDV ***plus*** ddI	• Extensive pediatric experience • Delayed-release capsules of ddI may allow once-daily dosing of ddI in older children able to swallow pills and who can receive adult dosing	• Bone marrow suppression with ZDV • Pancreatitis, neurotoxicity with ddI • ddI liquid formulation less palatable than 3TC or FTC liquid formulation • Food effect (ddI is recommended to be taken 1 hour before or 2 hours after food) – some experts give ddI without regard to food in infants or when compliance is an issue

NRTI: Nucleoside analogue reverse transcriptase inhibitor; NtRTI: Nucleotide analogue reverse transcriptase inhibitor
ABC: Abacavir; ddI: Didanosine; FTC: Emtricitabine; 3TC: Lamivudine; d4T: Stavudine; ZDV: Zidovudine

Table 5: Advantages and Disadvantages of Different Nucleoside or Nucleotide Analogue Reverse Transcriptase Inhibitor (NRTI, NtRTI) Backbone Combinations for Use in Highly Active Antiretroviral Combination Regimens for Initial Therapy in Children (cont'd) (Updated February 28, 2008)

	Advantages	Disadvantages
Use in Special Circumstances		
d4T ***plus*** 3TC ***or*** FTC	• Moderate pediatric experience • Palatable liquid formulations • Can give with food • FTC available as a palatable liquid formulation administered once daily	• d4T associated with higher incidence of hyperlactatemia/lactic acidosis, lipoatrophy, peripheral neuropathy, hyperlipidemia • Limited pediatric experience with d4T plus FTC
Insufficient Data to Make Recommendation		
Tenofovir-containing regimens in children in Tanner stages 1–3	• Resistance slow to develop • Once-daily dosing for tenofovir (adults) • Less mitochondrial toxicity than other NRTIs • Can give with food	• No pediatric formulation of tenofovir • Limited pediatric experience • Potential bone and renal toxicity; bone toxicity appears to be more frequent in younger children • Numerous drug-drug interactions with other antiretroviral agents including ddI, LPV/RTV, ATV, and TPV, complicating appropriate dosing
Not Recommended		
ZDV ***plus*** d4T	• None	• Pharmacologic and antiviral antagonism
3TC ***plus*** FTC	• None	• Similar drug structure • Single mutation (M184V) associated with resistance to both drugs
d4T ***plus*** ddI	• Has shown antiviral activity in small studies in children • Although not recommended for initial therapy, it may be considered for use in antiretroviral-experienced children who require a change in therapy	• Significant toxicities including lipoatrophy, peripheral neuropathy, hyperlactatemia including symptomatic and life-threatening lactic acidosis, hepatic steatosis, and pancreatitis

NRTI: Nucleoside analogue reverse transcriptase inhibitor; NtRTI: Nucleotide analogue reverse transcriptase inhibitor
ABC: Abacavir; ddI: Didanosine; FTC: Emtricitabine; 3TC: Lamivudine; d4T: Stavudine; ZDV: Zidovudine

Table 6: Advantages and Disadvantages of Different Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs) for Use in Highly Active Antiretroviral Combination Regimens for Initial Therapy in Children

(Updated February 28, 2008)

	Advantages	Disadvantages
General Issues		
NNRTI-Based Regimens	**NNRTI Class Advantages:** • Less dyslipidemia and fat maldistribution than protease inhibitors • Protease inhibitor sparing • Lower pill burden than protease inhibitors for those taking solid formulation; easier to use and adhere to than protease inhibitor-based regimens	**NNRTI Class Disadvantages:** • Single mutation can confer resistance, with cross-resistance between EFV and NVP • Rare but serious and potentially life-threatening cases of skin rash, including Stevens-Johnson syndrome, and hepatic toxicity with all NNRTIs (but highest with nevirapine) • Potential for multiple drug interactions due to metabolism via hepatic enzymes (e.g., CYP3A4)
Preferred		
Efavirenz (for children ≥3 years old and who can take capsules)	• Potent antiretroviral activity • Once-daily administration • Can give with food (but avoid high-fat meals)	• Neuropsychiatric side effects (bedtime dosing to reduce central nervous system effects) • Rash (generally mild) • No commercially available liquid • No data on dosing for children <3 years old • Teratogenic in primates; use with caution in adolescent females of childbearing age
Alternative		
Nevirapine (alternative NNRTI for children ≥3 years old; strongly recommended NNRTI for children <3 years old or who can't swallow capsules)	• Liquid formulation available • Dosing information for young infants available • Can give with food	• Higher incidence rash/ hypersensitivity reaction than other NNRTIs • Higher rates of serious hepatic toxicity than efavirenz • Need for initiating therapy with a lower dose and increasing in a stepwise fashion. This is to allow for auto-induction of NVP metabolism and is associated with a lower incidence of toxicity
Insufficient Data to Recommend		
Etravirine	• Three or more baseline NNRTI mutations result in a decreased virologic response • Patients with a history of NNRTI-related rash do not appear to be at increased risk of etravirine-related rash	• Limited data on pediatric dosing or safety • No pediatric formulation available • Food effect (should be given with food) • No data in treatment-naïve patients • Multiple drug interactions with PI's and other medications

NNRTI: Non-nucleoside analogue reverse transcriptase inhibitor; PI: Protease inhibitor

Table 7: Advantages and Disadvantages of Different Protease Inhibitors (PIs) for Use in Highly Active Antiretroviral Combination Regimens for Initial Therapy in Children (Updated February 23, 2009)

	Advantages	Disadvantages
General Issues		
Protease Inhibitor-Based Regimens	**Protease Class Advantages:** • NNRTI sparing • Clinical, virologic, and immunologic efficacy well documented • Resistance to protease inhibitors requires multiple mutations • Targets HIV at 2 steps of viral replication (viral reverse transcriptase and protease enzymes)	**Protease Class Disadvantages:** • Metabolic complications including dyslipidemia, fat maldistribution, insulin resistance • Potential for multiple drug interactions due to metabolism via hepatic enzymes (e.g., CYP3A4) • Higher pill burden than NRTI- or NNRTI-based regimens for those taking solid formulations • Poor palatability of liquid preparations, which may affect adherence to treatment regimen
Preferred		
Lopinavir/ ritonavir	• Coformulated liquid and tablet formulations • Tablets can be given without regard to food but may be better tolerated when taken with food or snack	• Poor palatability of liquid (bitter taste), although better than ritonavir alone • Food effect (liquid should be administered with food) • Ritonavir component associated with large number of drug interactions (see ritonavir)
Alternative		
Atazanavir in combination with low-dose ritonavir in children age ≥6 years	• Once-daily dosing • Atazanavir has less effect on triglyceride and total cholesterol levels than other PIs (but ritonavir boosting may be associated with elevations in these parameters)	• No liquid formulation • Food effect (should be administered with food) • Indirect hyperbilirubinemia common but asymptomatic • Use with caution in patients with pre-existing conduction system defects (can prolong PR interval of electrocardiogram)
Fosamprenavir in combination with low-dose ritonavir in children age ≥6 years	• Oral prodrug of amprenavir with lower pill burden • Pediatric formulation available • Can give with food	• Skin rash • More limited pediatric experience than preferred PI • Food effect (should be given with food) • Ritonavir component associated with large number of drug interactions (see ritonavir)
Nelfinavir in children age ≥2 years	• Powder formation (for liquid preparation or to be added to food) • Can give with food • Simplified 2 tablets (625mg) twice a day regimen has a reduced pill burden compared to other PI-containing regimens in older patients where the adult dose is appropriate	• Diarrhea • Powder formulation poorly tolerated • Food effect (should be administered with food) • Appropriate dosage for younger children not well defined • Need for 3 times daily dosing for younger children • Adolescents may require higher doses than adults

Table 7: Advantages and Disadvantages of Different Protease Inhibitors (PIs) for Use in Highly Active Antiretroviral Combination Regimens for Initial Therapy in Children (cont'd) (Updated February 23, 2009)

	Advantages	Disadvantages
Use in Special Circumstances		
Fosamprenavir (unboosted) in children age ≥2 years	• Oral prodrug of amprenavir with lower pill burden • Pediatric formulation available • Can give with food	• Skin rash • More limited pediatric experience than preferred PI • Food effect (should be given with food) • May require boosted regimen to achieve adequate plasma concentrations but pharmacokinetic data to define appropriate dosing not yet available
Atazanavir (unboosted) in treatment-naïve adolescents age ≥13 years and >39 kg, who are unable to tolerate ritonavir	• Once-daily dosing • Less effect on triglyceride and total cholesterol levels than other PIs	• No liquid formulation • Food effect (should be administered with food) • Indirect hyperbilirubinemia common but asymptomatic • Use with caution in patients with pre-existing conduction system defects (can prolong PR interval of electrocardiogram) • May require RTV boosting in treatment-naïve adolescent patients to achieve adequate plasma concentrations
Insufficient Data to Recommend		
Darunavir	• Effective in PI-experienced children when given with low-dose ritonavir boosting	• Pediatric data limited to antiretroviral-experienced children • Pediatric pill burden high with current tablet dose formulations • No liquid formulation • Food effect (should be given with food) • Must be given with ritonavir boosting to achieve adequate plasma concentrations • Contains sulfa moiety; potential for cross-sensitivity between darunavir and other drugs in sulfonamide class is unknown.
Tipranavir	• Effective in PI-experienced children and adults when given with low-dose ritonavir boosting • Liquid formulation	• Limited data in treatment-naïve patients • Food effect (should be administered with food) • Must be given with ritonavir boosting to achieve adequate plasma concentrations
Not Recommended		
Atazanavir (unboosted) in children <13 years and/or <39 kg	• Once-daily dosing (≥13 years) • Less effect on triglyceride and total cholesterol levels than other PIs	• Drug levels low if used without ritonavir boosting • No liquid formulation • Food effect (should be administered with food) • Indirect hyperbilirubinemia common but asymptomatic • Use with caution in patients with pre-existing conduction system defects (can prolong PR interval of electrocardiogram) • May require RTV boosting in treatment-naïve adolescent patients to achieve adequate plasma concentrations
Indinavir (unboosted)	• May be considered for use as component of a regimen in combination with low-dose ritonavir in postpubertal adolescents who weigh enough to receive adult dosing	• Only available in capsule • Possible higher incidence of nephrotoxicity in children • Requires 3-times daily dosing unless boosted with RTV • High fluid intake required to prevent nephrolithiasis • Food effect (should be taken 1 hour before or 2 hours after food) • Limited pediatric pharmacokinetic data
Ritonavir (full dose)	• Liquid formulation • Can be given with food	• Poor palatability of liquid (bitter taste) • Gastrointestinal intolerance • Food effect (should be administered with food) • Largest number drug interactions (most potent inhibitor of CYP3A4)

Table 7: Advantages and Disadvantages of Different Protease Inhibitors (PIs) for Use in Highly Active Antiretroviral Combination Regimens for Initial Therapy in Children (cont'd) (Updated February 23, 2009)

	Advantages	Disadvantages
Not Recommended (cont'd)		
Saquinavir (unboosted)		• Low bioavailability, should never be used as sole PI • Limited pediatric pharmacokinetic data; will require boosting with another PI (e.g., ritonavir) to achieve adequate concentrations • No liquid formulation • High pill burden • Must be taken with food • Photosensitivity reactions can occur

Table 8: Advantages and Disadvantages of Entry Inhibitors for Use in Highly Active Antiretroviral Combination Regimens (Updated February 28, 2008)

	Advantages	Disadvantages
General Issues		
Entry Inhibitors	**Entry Inhibitor Class Advantages:** • Susceptibility of HIV to a new class of antiretroviral	**Entry Inhibitor Class Disadvantages:** • Rapid development of resistance with enfuvirtide • CCR5 inhibitors ineffective against CXCR4 virus or mixed CCR5 and CXCR4 viral populations or dual tropic virus
Use in Special Circumstances		
Enfuvirtide	• Susceptibility of HIV to a new class of antiretroviral • Route of administration assure adequate drug levels	• Twice-daily subcutaneous injections • 98%–100% incidence of local injection site reactions
Insufficient Data to Recommend		
Maraviroc	• Susceptibility of HIV to a new class of antiretroviral • Can give with food	• Ineffective against CXCR4 or mixed/dual tropic viral populations • Limited data on pediatric dosing or safety • No pediatric formulation

Table 9: Advantages and Disadvantages of Integrase Inhibitors for Use in Highly Active Antiretroviral Combination Regimens (Updated February 28, 2008)

	Advantages	Disadvantages
General Issues		
Integrase Inhibitors	**Integrase Inhibitor Class Advantages:** • Susceptibility of HIV to a new class of antiretroviral	**Integrase Inhibitor Class Disadvantages:** • Limited data on pediatric dosing or safety
Insufficient Data to Recommend		
Raltegravir	• Susceptibility of HIV to a new class of antiretroviral • Can give with food	• Limited data on pediatric dosing or safety • No pediatric formulation • Rare systemic allergic reaction or hepatitis

Table 10: Example of Minimum Schedule for Monitoring of Children on Antiretroviral Therapy (Updated February 28, 2008)

Time after Starting Therapy	Toxicity Monitoring[1]	Adherence and Efficacy Monitoring
Baseline (prior to initiation of therapy)	Clinical history, complete blood count and differential, chemistries[3]	$CD4^+$ cell count/percentage, HIV RNA
1–2 weeks[2]	Clinical history	Adherence screen
4–8 weeks	Clinical history, complete blood count and differential, chemistries[3]	Adherence screen, $CD4^+$ cell count/percentage, HIV RNA
Every 3–4 months	Clinical history, complete blood count and differential, chemistries[3]	Adherence screen, $CD4^+$ cell count/percentage, HIV RNA
Every 6–12 months	Lipid Panel	

[1] For children receiving nevirapine, serum transaminase levels should be measured every 2 weeks for the first 4 weeks of therapy, then monthly for 3 months, followed by every 3 to 4 months.

[2] Children starting a new antiretroviral regimen should be evaluated in person or by a phone call within 1 to 2 weeks of starting medication to screen for clinical side effects and to ensure that they are taking medication properly; many clinicians will plan additional contacts (in person or by telephone) with the child and caregivers to support adherence during the first few weeks of therapy.

[3] Chemistries may include electrolytes, glucose, liver function tests (hepatic transaminases and bilirubin), renal function tests (BUN, creatinine), calcium, and phosphate. Additional evaluations should be tailored to the particular drugs the child is receiving; for example, pancreatic enzymes (amylase and lipase) may be considered if the child is starting drugs with potential pancreatic toxicity, such as ddI.

Table 11: Strategies to Improve Adherence with Antiretroviral Medications
(Updated October 26, 2006)

Initial Intervention Strategies
• Establish trust and identify mutually acceptable goals for care.
• Obtain explicit agreement on need for treatment and adherence.
• Identify depression, low self-esteem, drug use, or other mental health issues for the child/adolescent and/or caregiver that may decrease adherence. Treat prior to starting antiretroviral drugs, if possible.
• Identify family, friends, health team members, or others who can help with adherence support.
• Educate patient and family about the critical role of adherence in therapy outcome.
• Specify the adherence target: 95% of prescribed doses.
• Educate patient and family about the relationship between partial adherence and resistance.
• Educate patient and family about resistance and constraint of later choices of antiretroviral drug; i.e., explain that although a failure of adherence may be temporary, the effects on treatment choice may be permanent.
• Develop a treatment plan that the patient and family understand and to which they feel committed.
• Establish readiness to take medication by practice sessions or other means.
• Consider a brief period of hospitalization at start of therapy in selected circumstances, for patient education and to assess tolerability of medications chosen.
Medication Strategies
• Choose the simplest regimen possible, reducing dosing frequency and number of pills.
• Choose a regimen with dosing requirements that best conform to the daily and weekly routines and variations in patient and family activities.
• Choose the most palatable medicine possible (pharmacists may be able to add syrups or flavoring agents to increase palatability).
• Choose drugs with the fewest side effects; provide anticipatory guidance for management of side effects.
• Simplify food requirements for medication administration.
• Prescribe drugs carefully to avoid adverse drug-drug interactions.
Follow-up Intervention Strategies
• Monitor adherence at each visit and in between visits by telephone or letter as needed.
• Provide ongoing support, encouragement, and understanding of the difficulties of the demands of attaining >95% adherence with medication doses.
• Use patient education aids including pictures, calendars, stickers.
• Use pill boxes, reminders, alarms, pagers, timers.
• Provide nurse, social worker, or other practitioner adherence clinic visits or telephone calls.
• Provide access to support groups, peer groups, or one-on-one counseling for caregivers and patients, especially for those with known depression or drug use issues that are known to decrease adherence.
• Provide pharmacist-based adherence support.
• Consider gastrostomy tube use in selected circumstances.
• Consider a brief period of hospitalization for selected circumstances of apparent virologic failure, to assess adherence and reinforce that medication adherence is fundamental to successful antiretroviral therapy.
• Consider directly observed therapy (DOT) at home, in the clinic, or during a brief inpatient hospitalization.

Table 12: Considerations for Changing Antiretroviral Therapy for Human Immunodeficiency Virus (HIV)-Infected Children (Updated February 23, 2009)

Virologic Considerations*	• **Incomplete viralogic response to therapy:** Incomplete virologic response to therapy is defined for all children as a <1.0 $\log_{10}$ decrease in HIV RNA copy number from baseline after 8–12 weeks of therapy, HIV RNA >400 copies/mL after 6 months of therapy, or repeated HIV RNA above the level of detection of detection using the most sensitive assay after 12 months of therapy.† • **Viral rebound:** For children who have previously achieved undetectable plasma viral load in response to therapy, viral rebound is defined as subsequent, repeated detection of plasma HIV RNA on ultrasensitive PCR assays. Infrequent episodes of low level viremia (<1,000 copies/mL) are common and not generally reflective of virologic failure, whereas repeated or persistent viremia (especially if >1,000 copies/mL) more likely represents viral rebound. §
Immunologic Considerations*	• **Incomplete immunologic response to therapy:** Failure by a child <5 years old with severe immune suppression (CD4 percentage <15%) to improve CD4 values by ≥5 percentage points, or a failure by a child age 5 years old or older with severe immune suppression (CD4 <200 cells/mm^3) to improve CD4 values by ≥50 cells/mm^3 above baseline within the first year of therapy. • **Immunologic decline:** Sustained decline of 5 percentage points in CD4 percentage below pretherapy baseline at any age, or decline to below pretherapy baseline in absolute CD4 cell count in children who are age 5 years and older. **
Clinical Considerations	• **Progressive neurodevelopmental deterioration:** Two or more of the following on repeated assessments: impairment in brain growth, decline of cognitive function documented by psychometric testing, or clinical motor dysfunction. • **Growth failure:** Persistent decline in weight-growth velocity despite adequate nutritional support and without other explanation. • **Severe or recurrent infection or illness:** Recurrence or persistence of AIDS-defining conditions or other serious infections.

* At least two measurements (taken 1 week apart) should be performed before considering a change in therapy.

† The initial HIV RNA level of the child at the start of therapy and the level achieved with therapy should be considered when contemplating potential drug changes. For example, an immediate change in therapy may not be warranted if there is a sustained 1.5–2.0 $\log_{10}$ decrease in HIV RNA copy number, even if RNA remains detectable at low levels. Additionally, virologic suppression may take longer in young children given their higher viral load at the time of initiation of therapy than in older children or adults.

§ Continued observation with more frequent evaluation of HIV RNA levels should be considered if the HIV RNA increase is limited (i.e., <5,000 copies/mL), especially in children with limited treatment options. The presence of repeatedly detectable or increasing RNA levels suggests the development of resistance mutations and/or nonadherence.

** Declines that represent a change to a more advanced category of immunosuppression compared to baseline (e.g., from CD4 percentage of 28% to 23%, or from CD4 count of 250 cells/mm^3 to 150 cells/mm^3) or to more severe immunosuppression in those already suppressed at baseline (e.g., from CD4 percentage of 14% to 9%, or from CD4 count of 150 cells/mm^3 to 100 cells/mm^3) are of particular concern.

Table 13: Assessment of Antiretroviral Treatment Failure
(Updated February 23, 2009)

Assessment	Method	Intervention
Adherence	1. Interview child and caretaker • 24-hour or 7-day recall • Description of: o *WHO* gives medication o *WHAT* is given (names, doses) o *WHERE* medications are kept, administered o *WHEN* they are taken/given • Open-ended discussion of experiences taking/giving medications and barriers/challenges 2. Review pharmacy records • Assess timeliness of refills 3. Observe medication administration • Observe dosing/administration in clinic • Home based observation by visiting health professional • Hospital admission for trial of therapy o Observe administration/tolerance monitor treatment response 4. Psychosocial assessment • Comprehensive family-focused assessment of factors likely to impact on adherence with particular attention toward recent changes: o Status of caregiver, financial stability, housing, intimate relationships o School and achievement o Substance abuse (child, caretaker, family members) o Mental health and behavior o Child/youth and caretaker beliefs toward antiretroviral therapy o Disclosure status (to child and others)	Identify or re-engage family members to support/supervise adherence. Establish fixed daily times and routines for medication administration. Avoid confusion with drug names by explaining that drug therapies have generic names, trade names, and many agents are coformulated under a third or fourth name. Explore opportunities for facility or home-based DOT. Simplify medication regimen if feasible. Substitute new agents if single antiretroviral is poorly tolerated. Consider gastric tube placement to facilitate adherence. DOT. Utilization of tools to simplify administration (pill boxes, reminders including alarms, integrated medication packaging for AM or PM dosing, others). Relaxation techniques. Address competing needs through appropriate social services. Address and treat concomitant mental illness and behavioral disorders. Initiate disclosure discussions with family/child. Consider need for child protection services and alternate care settings when necessary.
Pharmaco-kinetics and Dosing	1. Recalculate doses for individual medications using weight or body surface area. 2. Identify concomitant medications including prescription, over-the-counter, and recreational substances; assess for drug-drug interactions. 3. Consider drug levels for specific antiretroviral drugs (see **Role of Therapeutic Drug Monitoring in Management of Treatment Failure**).	Adjust drug doses. Discontinue or substitute competing medications. Reinforce applicable food restrictions.
Resistance Testing	1. Genotypic and phenotypic resistance assays (see **Antiretroviral Drug-Resistance Testing**). 2. Tropism assay, as appropriate.	

Table 14. Options for Regimens with at Least Two Fully Active Agents Following Failure of Antiretroviral Regimen with Evidence for Viral Resistance to Therapy with Goal of Virologic Suppression * (Updated February 23, 2009)

Prior Regimen	Recommended Change
2 NRTIs + NNRTI	• 2 NRTIs (based on resistance testing) + PI
2 NRTIs + PI	• 2 NRTIs (based on resistance testing) + NNRTI • 2 NRTIs (based on resistance testing) + alternative PI (with low-dose ritonavir boosting, based on resistance testing) • NRTI(s) (based on resistance testing) + NNRTI + alternative PI (with low-dose ritonavir boosting, based on resistance testing)
3 NRTIs	• 2 NRTIs (based on resistance testing) + [NNRTI *or* PI] • NRTI(s) (based on resistance testing) + [NNRTI + PI]
Failed regimens including NRTI, NNRTI, PI	• >1 NRTI (based on resistance testing) + a newer PI (with low-dose ritonavir boosting, based on resistance testing) • >1 NRTI + dual-boosted PI (LPV/r + SQV, LPV/r + ATV) (consider adding either one or more of enfuvirtide, etravirine, or an integrase inhibitor) • NRTI(s) + ritonavir-boosted, potent PI (based upon resistance testing) + etravirine • NRTI(s) + ritonavir-boosted, potent PI (based upon resistance testing) + enfuvirtide and/or CCR5 antagonist and/or integrase inhibitor • If patient refuses PI and/or ritonavir boosting: NRTI(s) + enfuvirtide and/or integrase inhibitor and/or CCR5 antagonist

* Antiretroviral regimens should be chosen based on treatment history and drug-resistance testing to optimize antiretroviral drug effectiveness in the second regimen. This is particularly important in selecting NRTI components of an NNRTI-based regimen where drug resistance may occur rapidly to the NNRTI if the virus is not sufficiently sensitive to the NRTIs. Regimens should contain at least two, but preferably three, fully active drugs for durable, potent virologic suppression.

Table 15. Suggested Minimum Target Trough Concentrations (From *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents* - Table 10) (Updated November 3, 2008)

Drug	Concentration (ng/mL)
Fosamprenavir	400 (measured as amprenavir concentration)
Atazanavir	150
Indinavir	100
Lopinavir	1,000
Nelfinavir (Measurable active [M8] metabolite)	800
Saquinavir	100–250
Efavirenz	1,000
Nevirapine	3,000
Recommendations applicable only to treatment-experienced persons who have resistant HIV-1 strains	
Maraviroc	>50
Tipranavir	20,500

Appendix Table 1: Likelihood of Developing AIDS or Death Within 12 Months, by Age and CD4$^+$ T-Cell Percentage or Log_{10} HIV-1 RNA Copy Number in HIV-Infected Children Receiving No Therapy or Zidovudine Monotherapy

(Updated February 28, 2008)

	CD4 Percentage				Log_{10} HIV RNA Copy Number		
Age	**10%**	**20%**	**25%**	**30%**	**6.0**	**5.0**	**4.0**
Percent Mortality (95% Confidence Interval)							
6 Months	28.7	12 .4	8.5	6.4	9.7	4.1	2.7
1 Year	19.5	6.8	4.5	3.3	8.8	3.1	1.7
2 Years	11.7	3.1	2.0	1.5	8.2	2.5	1.1
5 Years	4.9	0.9	0.6	0.5	7.8	2.1	0.7
10 Years	2.1	0.3	0.2	0.2	7.7	2.0	0.6
Percent Developing AIDS (95% Confidence Interval)							
6 Months	51.4	31.2	24.9	20.5	23.7	13.6	10.9
1 Year	40.5	20.9	15.9	12.8	20.9	10.5	7.8
2 Years	28.6	12 .0	8.8	7.2	18.8	8.1	5.3
5 Years	14.7	4.7	3.7	3.1	17.0	6.0	3.2
10 Years	7.4	2.2	1.9	1.8	16.2	5.1	2.2

Table modified from: HIV Paediatric Prognostic Markers Collaborative Study Group. *Lancet* 2003; 362:1605-11.

Appendix Table 2: Death and AIDS/Death Rate per 100 Person-Years by Current Absolute CD4 Count and Age in HIV-Infected Children Receiving No Therapy or Zidovudine Monotherapy (HIV Paediatric Prognostic Markers Collaborative Study) and Adult Seroconverters (CASCADE Study)* (Updated February 28, 2008)

Age (Years)	Absolute CD4 cell count (cells/mm^3)					
	<50	50–99	100–199	200–349	350–499	500+
	Rate of Death Per 100 Patient-Years					
0–4	59.3	39.6	25.4	11.1	10.0	3.5
5–14	28.9	11.8	4.3	0.89	0.00	0.00
15–24	34.7	6.1	1.1	0.71	0.58	0.65
25–34	47.7	10.8	3.7	1.1	0.38	0.22
35–44	58.8	15.6	4.5	0.92	0.74	0.85
45–54	66.0	18.8	7.7	1.8	1.3	0.86
55+	91.3	21.4	17.6	3.8	2.5	0.91
	Rate of AIDS or Death per 100 Patient-Years					
0–4	82.4	83.2	57.3	21.4	20.7	14.5
5–14	64.3	19.6	16.0	6.1	4.4	3.5
15–24	61.7	30.2	5.9	2.6	1.8	1.2
25–34	93.2	57.6	19.3	6.1	2.3	1.1
35–44	88.1	58.7	25.5	6.6	4.0	1.9
45–54	129.1	56.2	24.7	7.7	3.1	2.7
55+	157.9	42.5	30.0	10.0	5.1	1.8

* Modifed from HIV Paediatric Prognostic Markers Collaborative Study and the CASCADE Collaboration. *J Infect Dis* 2008 in press.

Appendix Table 3: Association of Baseline Human Immunodeficiency Virus (HIV) RNA Copy Number and CD4+ T-Cell Percentage with Long-Term Risk for Death in HIV-Infected Children* (Updated April 17, 1998)

Baseline HIV RNA§ (copies/mL)/Baseline CD4+ T-cell percentage	No. patients¶	Deaths†	
		No.	(%)
≤ 100,000			
≥ 15%	103	15	(15%)
< 15%	24	15	(63%)
> 100,000			
≥ 15%	89	32	(36%)
< 15%	36	29	(81%)

* Data from the National Institute of Child Health and Human Development Intravenous Immunoglobulin Clinical Trial.

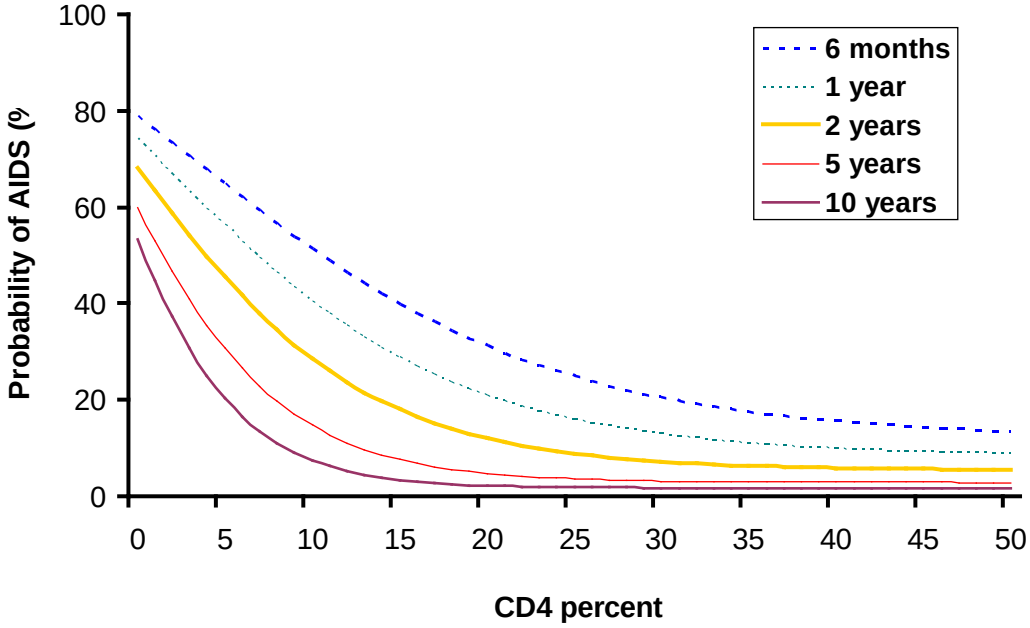
† Mean follow-up: 5.1 years.

§ Tested by NASBA® assay (manufactured by Organon Teknika, Durham, North Carolina) on frozen stored serum.

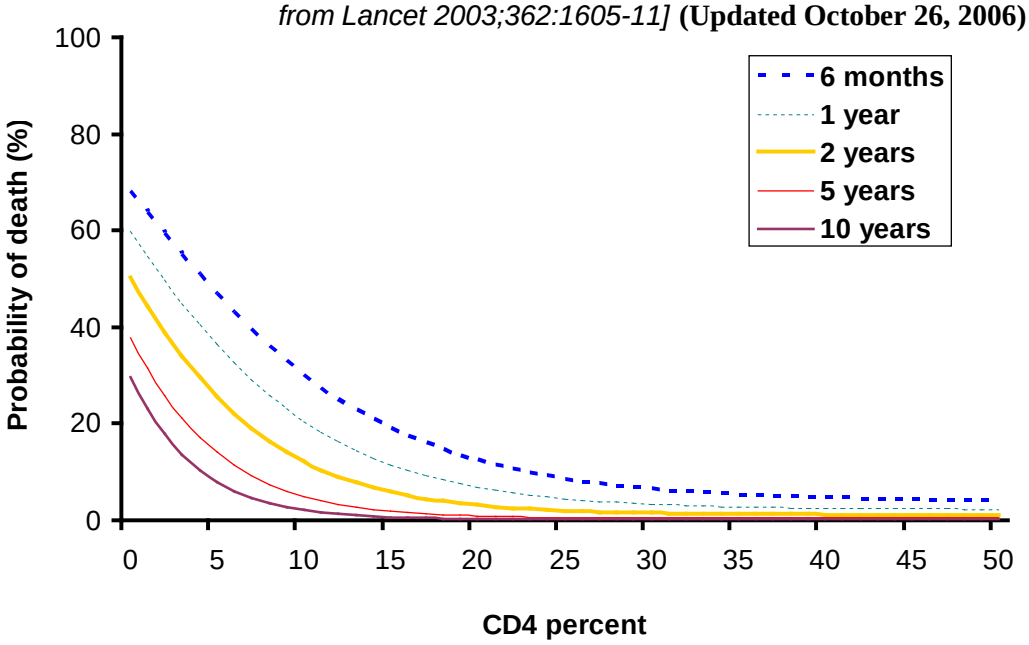
¶ Mean age: 3.4 years.

Source: Mofenson LM, Korelitz J, Meyer WA, et al. The relationship between serum human immunodeficiency virus type 1 (HIV-1) RNA level, CD4 lymphocyte percent, and long-term mortality risk in HIV-1-infected children. *J Infect Dis*, 1997. 175(5):1029–38.

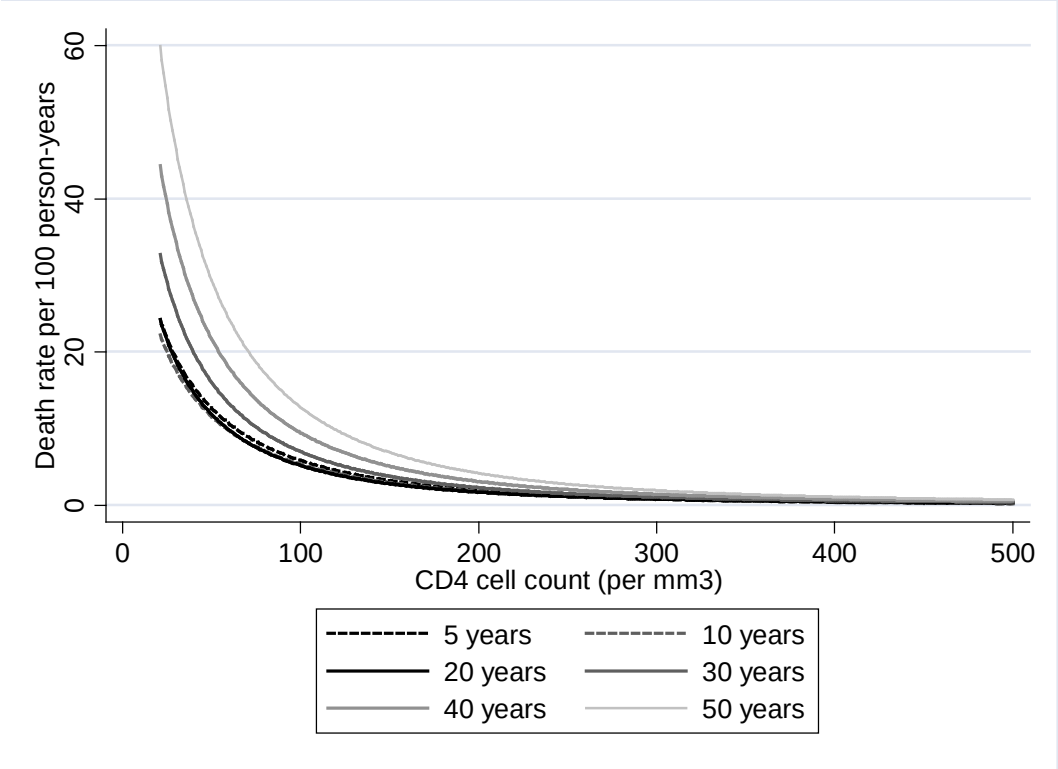
Appendix Figure 1: Estimated probability of AIDS within 12 months by age and CD4 percentage in HIV-infected children receiving no therapy or zidovudine monotherapy *[modified from Lancet 2003;362:1605-11]* **(Updated October 26, 2006)**



Appendix Figure 2: Estimated probability of death within 12 months by age and CD4 percentage in HIV-infected children receiving no therapy or zidovudine monotherapy *[modified from Lancet 2003;362:1605-11]* **(Updated October 26, 2006)**

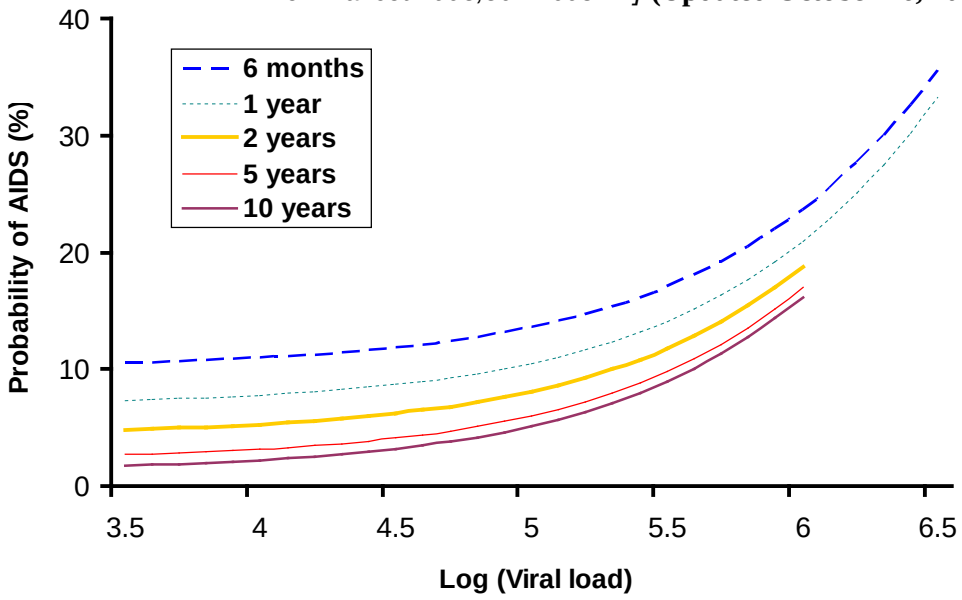


Appendix Figure 3: Death Rate per 100 Person-Years in HIV-Infected Children Age 5 Years or Older in the HIV Pediatric Prognostic Marker Collaborative Study and HIV-Infected Seroconverting Adults from the CASCADE Study* **(Updated February 28, 2008)**



* Modifed from HIV Paediatric Prognostic Markers Collaborative Study and the CASCADE Collaboration. J Infect Dis 2008 in press.

Appendix Figure 4: Estimated probability of AIDS within 12 months by age and HIV RNA copy number in HIV-infected children receiving no therapy or zidovudine monotherapy *[modified from Lancet 2003;362:1605-11]* **(Updated October 26, 2006)**



Appendix Figure 5: Estimated probability of death within 12 months by age and HIV RNA copy number in HIV-infected children receiving no therapy or zidovudine monotherapy *[modified from Lancet 2003;362:1605-11]* **(Updated October 26, 2006)**