TABLE 1. 1994 Revised Human Immunodeficiency Virus Pediatric Classification System: Immune Categories Based on Age-specific $CD4^+$ T-lymphocyte and Percentage*

	<12 mos		1-5 yrs		6-12 yrs	
Immune Category	**No./μL**	**(%)**	**No./μL**	**(%)**	**No./μL**	**(%)**
Category 1: no suppression	≥1,500	(≥25%)	≥1,000	(≥25%)	≥500	(≥25 %)
Category 2 : moderate suppression	750-1,499	(15%-24%)	500-999	(15%-24%)	200-499	(15%-24%)
Category 3: severe suppression	<750	(<15%)	<500	(<15%)	<200	(<15%)

*** Modified from: CDC. 1994 Revised classification system for human immunodeficiency virus infection in children less than 13 years of age. *MMWR* 1994; 43 (No. RR-12): 1-10.**

TABLE 2. 1994 Revised Human Immunodeficiency Virus Pediatric 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 two 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/mm^3), or thrombocytopenia (<100,000/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)

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

* Modified from: CDC. 1994 Revised classification system for human immunodeficiency virus infection in children less than 13 years

TABLE 3. Association of Baseline CD4+ T-lymphocyte Percentage with Long-term Risk for Death in Human Immunodeficiency Virus (HIV)-infected Children*

		Deaths†	
Baseline	**No. Patients§**	**No.**	**(%)**
<5%	33	32	(97%)
5% - 9%	29	22	(76%)
10% - 14%	30	13	(43%)
15% - 19%	41	18	(44%)
20% - 24%	52	13	(25%)
25% -29%	49	15	(31%)
30% - 34%	48	5	(10%)
≥35%	92	30	(33%)

* Data from the National Institute of Child Health and Human Development Intravenous Immunoglobulin Clinical Trial.
† Mean follow-up: 5.1 years
§ Includes 374 patients for whom baseline CD4+ T-lymphocyte percentage data were available.

Source: Mofenson L, 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;175:1029-38

TABLE 4. Association of Baseline Human Immunodeficiency Virus (HIV) RNA Copy Number with Long-term Risk for Death in HIV-infected Children*

		Deaths†	
Baseline (copies/mL)§	**No. Patients¶**	**No.**	**(%)**
Undetectable (i.e., ≤4,000)	25	6	(24%)
4,001 – 50,000	69	19	(28%)
50,001 – 100,000	33	5	(15%)
100,001 – 500,000	72	29	(40%)
500,001 – 1,000,000	20	8	(40%)
>1,000,000	35	25	(71%)
Total	**254**	**92**	**(36%)**

* 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 Corporation, Durham, North Carolina) on frozen stored serum.
¶ Mean age: 3.4 years.

Source: Mofenson L, 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;175:1029-38.

TABLE 5. Association of Baseline Human Immunodeficiency Virus (HIV) RNA Copy Number and CD4+ T-lymphocyte Percentage with Long-term Risk for Death in HIV-infected Children*

		Deaths†	
Baseline HIV RNA§ (copies/mL) / Baseline CD4+ T-lymphocyte Percentage	**No. Patients¶**	**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 Corporation, Durham, North Carolina) on frozen stored serum.
¶ Mean age: 3.4 years.

Source: Mofenson L, 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;175:1029-38.

TABLE 6. Association of Baseline Human Immunodeficiency Virus (HIV) RNA Quartile by Age at Entry with Risk for Disease Progression or Death During Study Follow-up Among HIV-infected Children Receiving Antiretroviral Treatment*

		Disease Progression or Death	
Age at Entry / Baseline HIV RNA Quartiles (copies/mL)†	**No. Patients**	**No.**	**(%)**
<30 months§			
<1,000 – 150,000	79	9	(11%)
150,001 – 500,000	66	13	(20%)
500,001 – 1,700,000	76	29	(38%)
>1,700,000	81	42	(52%)
≥30 months¶			
<1,000 – 15,000	66	0	(0%)
15,001 – 50,000	54	7	(13%)
50,001 – 150,000	80	13	(16%)
>150,000	64	22	(34%)

* Data from the Pediatric AIDS Clinical Trial Group protocol 152.
† Tested by NASBA® assay (manufactured by Organon Teknika Corporation, Durham, North Carolina) on frozen stored serum.
§ Mean age: 1.1 years.
¶ Mean age: 7.3 years.

Source: Palumbo PE, Raskino C, Fiscus S, et al. Disease progression in HIV-infected infants and children: predictive value of quan-

TABLE 7. Indications for Initiation of Antiretroviral Therapy in Children with Human Immunodeficiency Virus (HIV) Infection*

- Clinical symptoms associated with HIV infection (i.e., clinical categories A, B, or C [Table 2]).
- Evidence of immune suppression, indicated by $CD4^+$ T- lymphocyte absolute number or percentage (i.e., immune category 2 or 3 [Table 1]).
- Age <12 months – regardless of clinical, immunologic, or virologic status.
- For asymptomatic children aged ≥1 year with normal immune status, two options can be considered:

  1. Preferred Approach

     Initiate therapy – regardless of age or symptom status.

  2. Alternative Approach

     Defer treatment in situations in which the risk for clinical diseaseprogression is low and other factors (e.g., concern for the durability of response, safety, and adherence) favor postponing treatment. In such cases, the health-care provider should regularly monitor virologic, immunologic, and clinical status. Factors to be considered in deciding to initiate therapy include the following:

     - High or increasing HIV RNA copy number.
     - Rapidly declining $CD4^+$ T-lymphocyte number or percentage to values approaching those indicative of moderate immune suppression (i.e., immune category 2 [Table 1]).
     - Development of clinical symptoms.

* Indications for initiation of antiretroviral therapy in post-pubertal HIV-infected adolescents should follow the adult guidelines (Office of Public Health and Science, Department of Health and Human Services. Availability of report of NIH panel to define principles of therapy of HIV infection and guidelines for the use of antiretroviral agents in HIV-infected adults. Federal Register 1997; 62:33417-8.)

TABLE 8. Recommended Antiretroviral Regimens for Initial Therapy for Human Immunodeficiency Virus (HIV) Infection in Children

Strongly Recommended

Clinical trial evidence of clinical benefit and/or sustained suppression of HIV replication in adults and/or children.

- One highly active protease inhibitor plus two nucleoside analogue reverse transcriptase inhibitors (NRTIs)
  - Preferred protease inhibitor for infants and children who cannot swallow pills or capsules: *nelfinavir or ritonavir*. Alternative for children who can swallow pills or capsules: *indinavir*.
  - Recommended dual NRTI combinations: the most data on use in children are available for the combinations of *zidovudine (ZDV) and dideoxyinosine (ddI) and for ZDV and lamivudine (3TC)*. More limited data are available for the combinations of *stavudine (d4T) and ddI, d4T and 3TC, and ZDV and zalcitabine (ddC).**
- Alternative for children who can swallow capsules: Efavirenz (Sustiva) ** plus 2 NRTIs (see above) or efavirenz (Sustiva) plus nelfinavir and 1 NRTI.

Recommended as an Alternative

Clinical trial evidence of suppression of HIV replication, but 1) durability may be less in adults and/or children than with strongly recommended regimens; or 2) the durability of suppression is not yet defined; or 3) evidence of efficacy may not outweigh potential adverse consequences (e.g., toxicity, drug interactions, cost, etc).

- *Nevirapine*[§] and two NRTIs.
- *Abacavir* in combination with ZDV and 3TC.

Offer only in Special Circumstances

Clinical trial evidence of 1) limited benefit for patients; or 2) data are inconclusive, but may be reasonably offered in special circumstances.

- Two NRTIs

Not Recommended

Evidence against use because of 1) overlapping toxicity; and/or 2) because use may be virologically undesirable.

- Any monotherapy[¶]
- d4T and ZDV
- ddC and ddI
- ddC and d4T
- ddC and 3TC

* ddC is not available in a liquid preparation commercially, although a liquid formulation is available through a compassionate use program of the manufacturer (Hoffman-LaRoche Inc., Nutley, New Jersey). ZDV and ddC is a less preferred choice for use in combination with a protease inhibitor.

[§] ~~A liquid preparation of nevirapine is not available commercially, but is available through a compassionate use program of the manufacturer (Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, Connecticut).~~

[¶] Except for ZDV chemoprophylaxis administered to HIV-exposed infants during the first 6 weeks of life to prevent perinatal HIV transmission; if an infant is identified as HIV-infected while receiving ZDV prophylaxis, therapy should be changed to a combination antiretroviral drug regimen.

** Efavirenz is currently available only in capsule form, but liquid preparation is currently being evaluated. There are currently no data on appropriate dosage of efavirenz in children under age 3 years.

TABLE 9. Considerations for Changing Antiretroviral Therapy for Human Immunodeficiency Virus (HIV)-infected Children

Virologic Considerations*

- Less than a minimally acceptable virologic response after 8-12 weeks of therapy. For children receiving antiretroviral therapy with two nucleoside analogue reverse transcriptase inhibitors (NRTIs) and a protease inhibitor, such a response is defined as a <10-fold (1.0 $\log_{10}$) decrease from baseline HIV RNA levels. For children who are receiving less potent antiretroviral therapy (i.e., dual NRTI combinations), an insufficient response is defined as a less than fivefold (0.7 $\log_{10}$) decrease in HIV RNA levels from baseline.
- HIV RNA not suppressed to undetectable levels after 4-6 months of antiretroviral therapy.†
- Repeated detection of HIV RNA in children who initially responded to antiretroviral therapy with undetectable levels.§
- A reproducible increase in HIV RNA copy number among children who have had a substantial HIV RNA response but still have low levels of detectable HIV RNA. Such an increase would warrant change in therapy if, after initiation of the therapeutic regimen, a greater than threefold (0.5 $\log_{10}$) increase in copy number for children aged $\geq$2 years and greater than fivefold (0.7 $\log_{10}$) increase is observed for children aged <2 years.

Immunologic Considerations*

- Change in immunologic classification (Table 1).¶
- For children with $CD4^+$ T-lymphocyte percentages of <15% (i.e., those in immune category 3), a persistent decline of five percentiles or more in $CD4^+$ cell percentage (e.g., from 15% to 10%).
- A rapid and substantial decrease in absolute $CD4^+$ T-lymphocyte count (e.g., a >30% decline in <6 months).

Clinical Considerations

- Progressive neurodevelopmental deterioration.
- Growth failure defined as persistent decline in weight-growth velocity despite adequate nutritional support and without other explanation.
- Disease progression defined as advancement from one pediatric clinical category to another (e.g., from clinical category A to clinical category B)**.

* 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 co templating potential drug changes. For example, an immediate change in therapy may not be warranted if there is a sustained 1.5 to 2.0 $\log_{10}$ decrease in HIV RNA copy number, even if RNA remains detectable at low levels.

§ More frequent evaluation of HIV RNAlevels should be considered if the HIV RNA increase is limited (e.g., if when using an HIV RNA assay with a lower limit of detection of 1,000 copies/mL, there is a $\leq$0.7 $\log_{10}$ increase from undetectable to approximately 5,000 copies/mL in an infant aged <2 years).

¶ Minimal changes in $CD4^+$ T-lymphocyte 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 $CD4^+$ percentile within the same immunologic category (e.g., a drop from 35% to 25%).

** In patients with stable immunologic and virologic parameters, progression from one clinical category to another may not represent an indication to change therapy. Thus, in patients whose disease progression is not associated with neurologic deterioration or growth failure, virologic and immunologic considerations are important in deciding whether to change therapy.