Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

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Table 1. Outline of the Guidelines Development Process

Topic	Comment
Goal of the guidelines	Provide guidance to HIV care practitioners on the optimal use of antiretroviral (ARV) agents in HIV-1-infected infants, children, and adolescents (through puberty) in the United States.
Panel members	The Panel is composed of approximately 25 voting members who have expertise in management of HIV infection in infants, children, and adolescents. Members include representatives from the Committee on Pediatric AIDS of the American Academy of Pediatrics and community representatives with knowledge of pediatric HIV infection. The Panel also includes at least one representative from each of the following Department of Health and Human Services (HHS) agencies: Centers for Disease Control and Prevention (CDC), Food and Drug Administration (FDA), Health Resources and Services Administration (HRSA), and the National Institutes of Health (NIH). A representative from the Canadian Pediatric AIDS Research Group participates as a nonvoting, ex officio member of the Panel. The U.S. government representatives are appointed by their respective agencies; nongovernmental members are selected after an open announcement to call for nominations. Each member serves on the Panel for a 3-year term with an option for reappointment. A list of current members can be found in the Panel Roster.
Financial disclosure	All members of the Panel submit a financial disclosure statement in writing annually, reporting any association with manufacturers of ARV drugs or diagnostics used for management of HIV infections. A list of the latest disclosures is available on the AIDS*info* website (http://aidsinfo.nih.gov).
Users of the guidelines	Providers of care to HIV-infected infants, children, and adolescents
Developer	Panel on Antiretroviral Therapy and Medical Management of HIV-Infected Children—a working group of OARAC
Funding source	Office of AIDS Research, NIH and Health Resources and Services Administration
Evidence collection	A standardized review of recent relevant literature related to each section of the guidelines is performed by a representative of the Francois-Xavier Bagnoud Center and provided to individual Panel section working groups. The recommendations are generally based on studies published in peer-reviewed journals. On some occasions, particularly when new information may affect patient safety, unpublished data presented at major conferences or prepared by the FDA and/or manufacturers as warnings to the public may be used as evidence to revise the guidelines.
Recommendation grading	Described in Table 2.
Method of synthesizing data	Each section of the guidelines is assigned to a small group of Panel members with expertise in the area of interest. The members synthesize the available data and propose recommendations to the Panel. The Panel discusses and votes on all proposals during monthly teleconferences. Proposals endorsed by a consensus of members are included in the guidelines as official Panel recommendations.
Other guidelines	These guidelines focus on HIV-infected infants, children, and adolescents through puberty. For more detailed discussion of issues of treatment of postpubertal adolescents, the Panel defers to the designated expertise offered by the Panel on Antiretroviral Guidelines for Adults and Adolescents. Separate guidelines outline the use of antiretroviral therapy (ART) in HIV-infected pregnant women and interventions for prevention of mother-to-child transmission (PMTCT), ART for nonpregnant HIV-infected adults and postpubertal adolescents, and ARV prophylaxis for those who experience occupational or nonoccupational exposure to HIV. These guidelines are also available on the AIDS*info* website (http://aidsinfo.nih.gov).

Table 1. Outline of the Guidelines Development Process, cont'd

Topic	Comment
Update plan	The Panel meets monthly by teleconference to review data that may warrant modification of the guidelines. Updates may be prompted by new drug approvals (or new indications, formulations, or frequency of dosing), new significant safety or efficacy data, or other information that may have a significant impact on the clinical care of patients. In the event of significant new data that may affect patient safety, the Panel may issue a warning announcement and post accompanying recommendations on the AIDS*info* website until the guidelines can be updated with appropriate changes.
Public comments	A 2-week public comment period follows release of the updated guidelines on the AIDS*info* website. The Panel reviews comments received to determine whether additional revisions to the guidelines are indicated. The public may also submit comments to the Panel at any time at contactus@aidsinfo.nih.gov.

Table 2. Rating Scheme for Recommendations

Strength of Recommendation	Quality of Evidence for Recommendation
A: Strong recommendation for the statement **B:** Moderate recommendation for the statement **C:** Optional recommendation for the statement	**I:** One or more randomized trials in children† with clinical outcomes and/or validated laboratory endpoints **I*:** One or more randomized trials in adults with clinical outcomes and/or validated laboratory endpoints plus accompanying data in children† from one or more well-designed, non-randomized trials or observational cohort studies with long-term clinical outcomes **II:** One or more well-designed, non-randomized trials or observational cohort studies in children† with long-term clinical outcomes **II*:** One or more well-designed, non-randomized trials or observational cohort studies in adults with long-term clinical outcomes plus accompanying data in children† from one or more smaller non-randomized trials or cohort studies with clinical outcome data **III:** Expert opinion

† Studies that include children or children and adolescents but not studies limited to postpubertal adolescents

Table 3. 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

	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;362:1605-1611.

Table 4. Death and AIDS/Death Rate per 100 Person-Years by Current Absolute CD4 Cell Count and Age in HIV-Infected Children Receiving No Therapy or Zidovudine Monotherapy (HIV Paediatric Prognostic Markers Collaborative Study) and Adult Seroconverters (CASCADE Study)

	Absolute CD4 Cell Count (cells/mm^3)					
Age (Years)	**<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

Table modified from: HIV Paediatric Prognostic Markers Collaborative Study and the CASCADE Collaboration. *J Infect Dis*. 2008;197:398-404.

Table 5. Association of Baseline Human Immunodeficiency Virus (HIV) RNA Copy Number and CD4 T-Cell Percentage with Long-Term Risk of Death in HIV-Infected Children[a]

		Deaths[b]	
Baseline HIV RNA[c] (copies/mL) / Baseline CD4 T-cell percentage	**No. Patients[d]**	**No.**	**(%)**
≤ 100,000			
≥ 15%	103	15	(15%)
< 15%	24	15	(63%)
> 100,000			
≥ 15%	89	32	(36%)
< 15%	36	29	(81%)

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

[b] Mean follow-up: 5.1 years.

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

[d] 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):1029–1038.

Figure 1. Estimated Probability of AIDS Within 12 Months of Age and CD4 Percentage in HIV-Infected Children Receiving No Therapy or Zidovudine Monotherapy

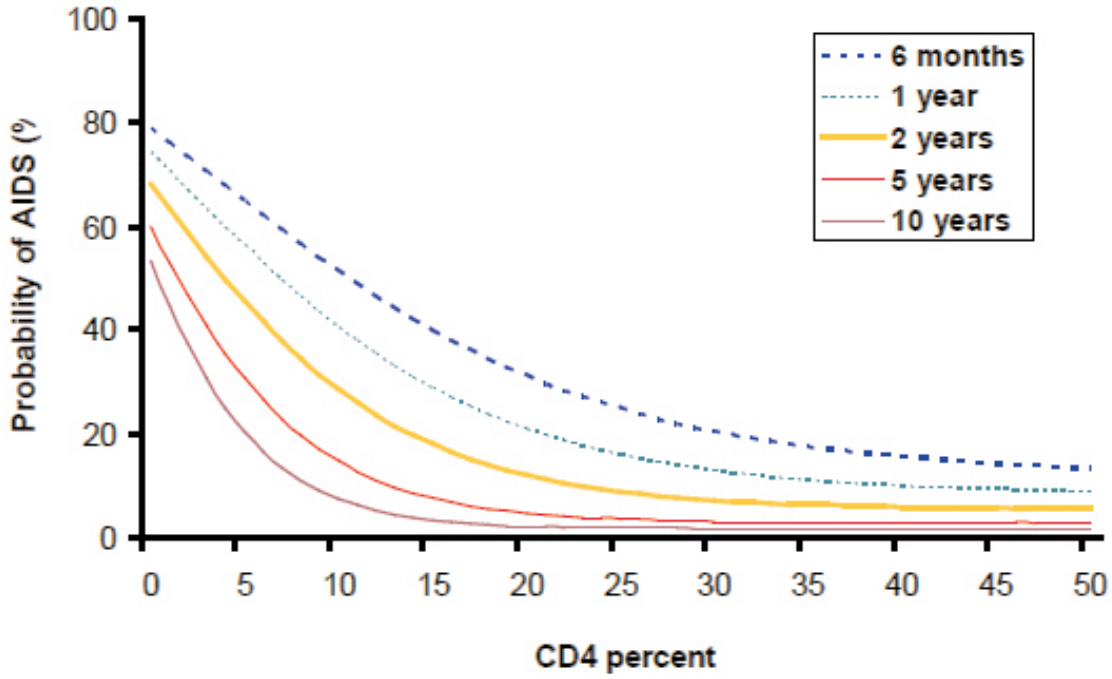

Table modified from: *Lancet* 2003;362:1605-1611

Figure 2. Estimated Probability of Death Within 12 Months of Age and CD4 Percentage in HIV-Infected Children Receiving No Therapy or Zidovudine Monotherapy

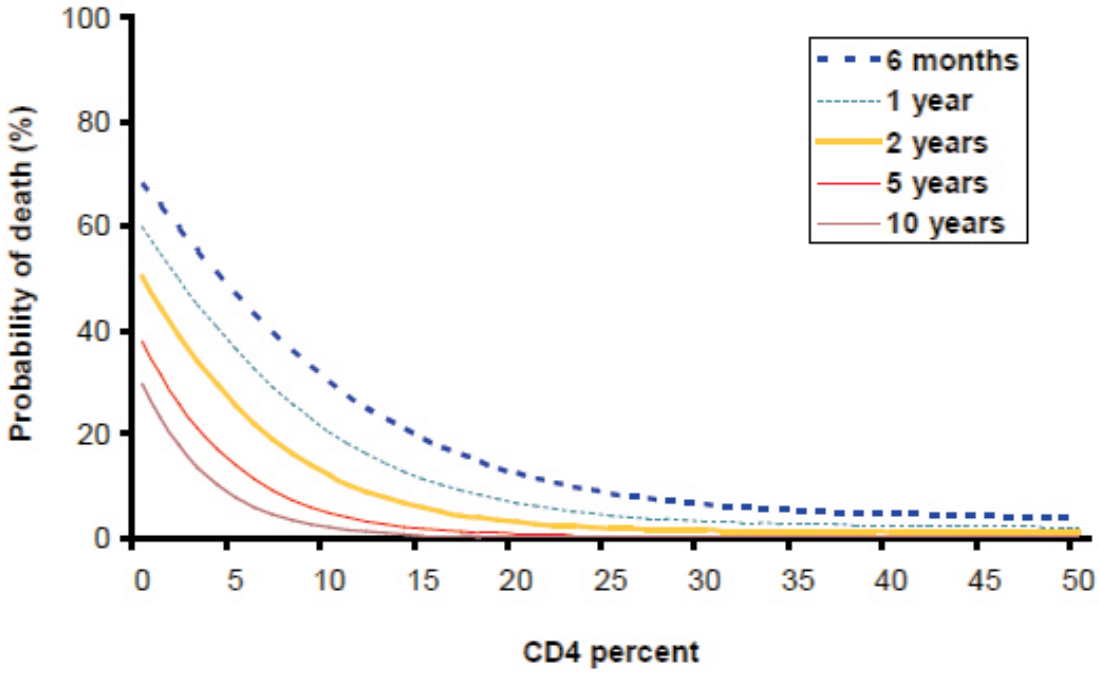

Table modified from: *Lancet* 2003;362:1605-1611

Figure 3. Death Rate per 100 Person-Years in HIV-Infected Children Age 5 Years or Older in the HIV Paediatric Prognostic Marker Collaborative Study and HIV-Infected Seroconverting Adults from the CASCADE Study

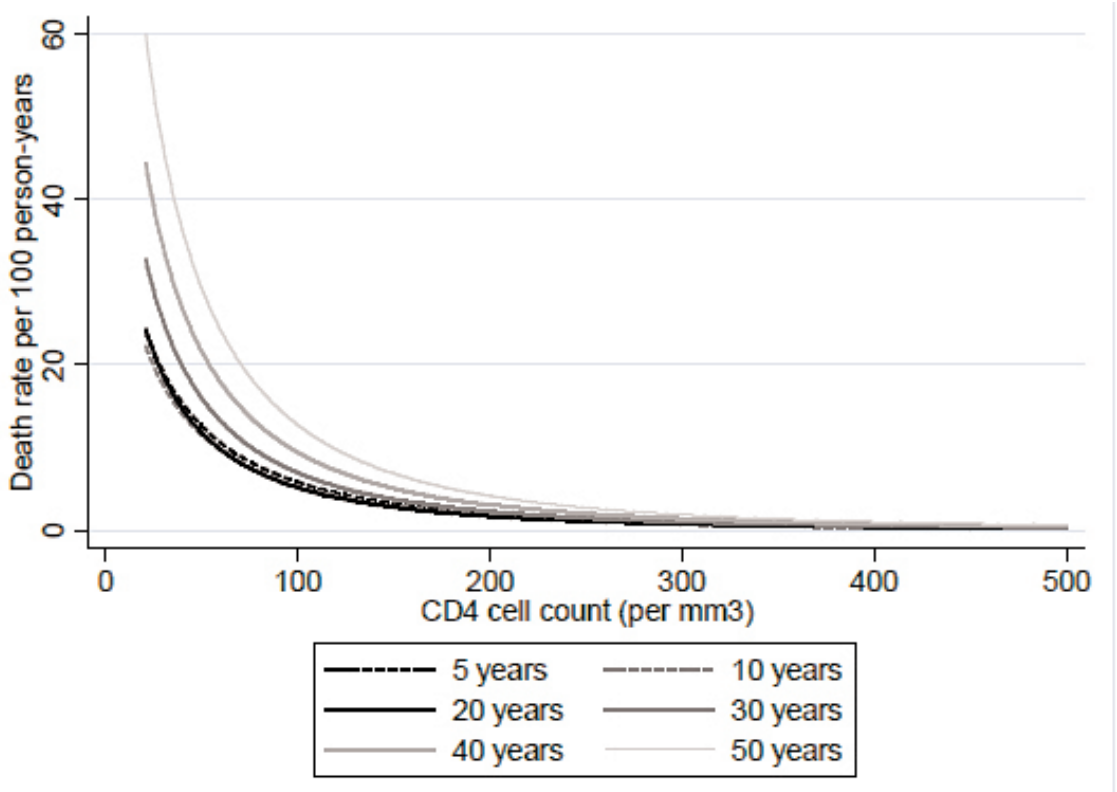

Figure modifed from: HIV Paediatric Prognostic Markers Collaborative Study and the CASCADE Collaboration. *J Infect Dis*. 2008;197:398-404.

Figure 4. Estimated Probability of AIDS Within 12 Months of Age and HIV RNA Copy Number in HIV-Infected Children Receiving No Therapy or Zidovudine Monotherapy

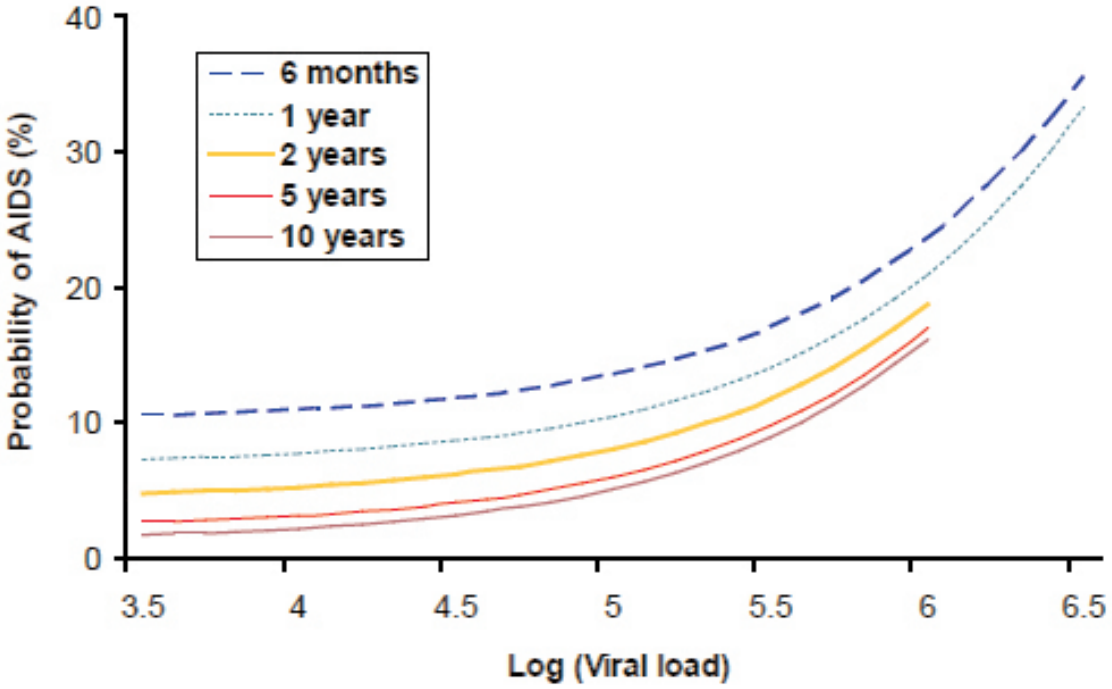

Table modified from: *Lancet* 2003;362:1605-1611

Figure 5. Estimated Probability of Death Within 12 Months of Age and HIV RNA Copy Number in HIV-Infected Children Receiving No Therapy or Zidovudine Monotherapy

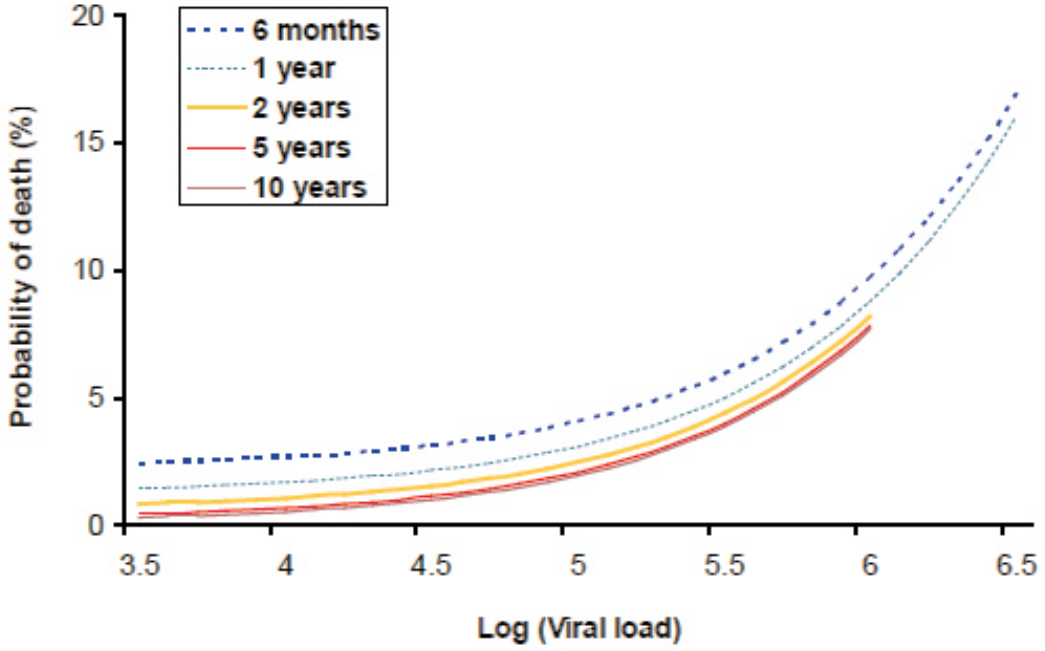

Table modified from: *Lancet* 2003;362:1605-1611

Table 6. 1994 Revised HIV Pediatric Classification System: Clinical Categories (page 1 of 2)

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 g/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 (that is, 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 (that is, more than two episodes within 1 year) • HSV bronchitis, pneumonitis, or esophagitis with onset before age 1 month • Herpes zoster (that is, 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 (that is, complicated chickenpox)

Table 6. 1994 Revised HIV Pediatric Classification System: Clinical Categories (page 2 of 2)

Category C: Severely Symptomatic

Children who have any condition listed in the 1987 surveillance case definition for AIDS (below), with the exception of LIP, which is a Category B condition:

- Serious bacterial infections, multiple or recurrent (that is, 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 aged <2 years); 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 aged >1 month
- Histoplasmosis, disseminated (at a site other than or in addition to lungs or cervical or hilar lymph nodes)
- Kaposi sarcoma
- Lymphoma, primary, in brain
- Lymphoma, small, noncleaved cell (Burkitt), or immunoblastic or large cell lymphoma of B-cell or unknown immunologic phenotype
- Mycobacterium tuberculosis, disseminated or extrapulmonary
- 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 jirovecii* pneumonia
- Progressive multifocal leukoencephalopathy
- Salmonella (nontyphoid) septicemia, 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 two of the following percentile lines on the weight-for-age chart (such as 95th, 75th, 50th, 25th, 5th) in a child ≥1 year of age; OR c) <5th percentile on weight-for-height chart on two consecutive measurements, ≥30 days apart **PLUS** 1) chronic diarrhea (that is, ≥ two loose stools per day for >30 days), **OR** 2) documented fever (for ≥30 days, intermittent or constant)

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.

Table 7. Indications for Initiation of Antiretroviral Therapy in HIV-Infected Children

Table 7 provides general guidance rather than absolute recommendations for individual patients. Factors to be considered in decisions about initiation of therapy include 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. Before making the decision to initiate therapy, the provider should fully assess, discuss, and address issues associated with adherence with a child (if age appropriate) and the caregiver. Patients/caregivers may choose to postpone therapy, and, on a case-by-case basis, providers may elect to defer therapy based on clinical and/or psychosocial factors.[a]

Age	Criteria	Recommendation
<12 months	• Regardless of clinical symptoms, immune status, or viral load	*Treat (**AI** for <12 weeks of age; **AII** for ≥12 weeks)*
1 to <3 years	• AIDS or significant HIV-related symptoms[b] • CD4 cell count <1000 cells/mm^3 *or* CD4 percentage <25%,[e] • Asymptomatic or mild symptoms[c] and ❍ CD4 cell count ≥1000 cells/mm^3 or percentage ≥25%	*Treat **(AI*)*** *Treat **(AII)*** *Consider Treatment*[d] ***(BIII)***
3 to <5 years	• AIDS or significant HIV-related symptoms[b] • CD4 cell count <750 cells/mm^3 *or* CD4 percentage <25%,[e] • Asymptomatic or mild symptoms[c] and ❍ CD4 cell count ≥750 cells/mm^3 or percentage ≥25%	*Treat **(AI*)*** *Treat **(AII)*** *Consider Treatment*[d] ***(BIII)***
≥5 years	• AIDS or significant HIV-related symptoms[b] • CD4 cell count ≤500 cells/mm^3,[e] • Asymptomatic or mild symptoms[c] and ❍ CD4 cell count >500 cells/mm^3	*Treat **(AI*)*** *Treat (**AI*** *for CD4 cell count <350 cells/mm^3 and **BII*** for CD4 cell count 350–500 cells/mm^3)* *Consider Treatment*[d] ***(BIII)***

Rating of Recommendations: *A = Strong; B = Moderate; C = Optional*

Rating of Evidence: *I = One or more randomized trials in children† with clinical outcomes and/or validated endpoints; I* = One or more randomized trials in adults with clinical outcomes and/or validated laboratory endpoints with accompanying data in children† from one or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes; II = One or more well-designed, nonrandomized trials or observational cohort studies in children† with long-term outcomes; II* = One or more well-designed, nonrandomized trials or observational studies in adults with long-term clinical outcomes with accompanying data in children† from one or more similar nonrandomized trials or cohort studies with clinical outcome data; III = expert opinion*

† Studies that include children or children and adolescents but not studies limited to postpubertal adolescents

[a] Children in whom ART is deferred need close follow-up. Factors to consider in deciding when to initiate therapy in children in whom treatment was deferred include:
- Increasing HIV RNA levels (such as HIV RNA levels approaching 100,000 copies/mL);
- CD4 cell count or percentage values approaching the age-related threshold for treatment;
- Development of clinical symptoms; and
- The ability of caregiver and child to adhere to the prescribed regimen.

[b] CDC Clinical Categories C and B (except for the following Category B condition: single episode of serious bacterial infection)

[c] CDC Clinical Category A or N or the following Category B condition: single episode of serious bacterial infection

[d] The rating of the evidence is stronger for treatment in this group of patients if plasma HIV RNA level is >100,000 copies/mL (BII)

[e] Laboratory data should be confirmed with a second test to meet the treatment criteria before initiation of ART.

Table 8. ARV Regimens Recommended for Initial Therapy for HIV Infection in Children (page 1 of 2)

A combination ARV regimen in treatment-naive children generally contains 1 NNRTI plus a 2-NRTI backbone or 1 PI plus a 2-NRTI backbone. Regimens should be individualized based on advantages and disadvantages of each combination (see Tables 10–14).

Preferred Regimens	
Children aged ≥14 days to <3 years[a]	Two NRTIs ***plus*** LPV/r
Children aged ≥3 years	Two NRTIs ***plus*** EFV[b] Two NRTIs ***plus*** LPV/r
Children aged ≥6 years	Two NRTIs ***plus*** ATV ***plus*** low-dose RTV Two NRTIs ***plus*** EFV[b] Two NRTIs ***plus*** LPV/r
Alternative Regimens	
Children of any age	Two NRTIs ***plus*** NVP[c]
Children aged ≥3 years	Two NRTIs ***plus*** DRV ***plus*** low-dose RTV
Children aged ≥6 months[d]	Two NRTIs ***plus*** FPV ***plus*** low-dose RTV
Regimens for Use in Special Circumstances	
Two NRTIs ***plus*** ATV unboosted (for treatment-naive adolescents aged ≥13 years and weight >39 kg) Two NRTIs ***plus*** FPV unboosted (children aged ≥2 years) Two NRTIs ***plus*** NFV (children aged ≥2 years) Zidovudine ***plus*** 3TC ***plus*** ABC	
2-NRTI Backbone Options for Use in Combination with Additional Drugs (in alphabetical order)	
Preferred	ABC ***plus*** (3TC ***or*** FTC) (children aged ≥3 months) TDF ***plus*** (3TC ***or*** FTC) (adolescents, Tanner Stage 4 or 5) ZDV ***plus*** (3TC ***or*** FTC)
Alternative	ddI ***plus*** (3TC ***or*** FTC) TDF ***plus*** (3TC ***or*** FTC) (adolescents,Tanner Stage 3) ZDV ***plus*** ABC ZDV ***plus*** ddI
Use in Special Circumstances	d4T ***plus*** (3TC ***or*** FTC) TDF ***plus*** (3TC ***or*** FTC) (prepubertal children aged ≥2 years and adolescents, Tanner Stage 1 or 2)
Not Recommended for Initial Therapy	
ETR-containing regimens EFV-containing regimens for children aged <3 years TPV-containing regimens SQV-containing regimens	

Table 8. ARV Regimens Recommended for Initial Therapy for HIV Infection in Children (page 2 of 2)

Not Recommended for Initial Therapy
IDV-containing regimens
Dual (full-dose) PI regimens
Full-dose RTV or use of RTV as the sole PI
Unboosted ATV-containing regimens in children aged <13 years and/or weight <39 kg
NFV-containing regimens for children aged <2 years
Unboosted DRV-containing regimens
Once-daily dosing of boosted DRV in children aged <12 years
Once-daily dosing of LPV/r or boosted or unboosted FPV
Triple-NRTI regimens other than ABC + ZDV + 3TC
Triple-class regimens, including NRTI ***plus*** NNRTI ***plus*** PI
Four-drug regimens with three NRTIs ***plus*** NNRTI
Regimens with dual-NRTI backbones of ABC + ddI, ABC + TDF, and ddI + TDF
TDF-containing regimens in children aged <2 years
MVC-containing regimens
RPV-containing regimens
RAL-containing regimens
T-20-containing regimens
EVG-containing regimens

[a] LPV/r should not be administered to neonates before a postmenstrual age (first day of the mother's last menstrual period to birth plus the time elapsed after birth) of 42 weeks and a postnatal age of at least 14 days.

[b] EFV should be used only in children aged ≥3 years with weight ≥10 kg. Unless adequate contraception can be ensured, EFV-based therapy is not recommended for adolescent females who are sexually active and may become pregnant.

[c] NVP should not be used in postpubertal girls with CD4 count >250/mm^3, unless the benefit clearly outweighs the risk.

[d] FPV with low dose ritonavir should only be administered to infants born at ≥38 weeks gestation who have attained a postnatal age of 28 days and to infants born before 38 weeks gestation who have reached a postmenstrual age of 42 weeks.

Key to Abbreviations: 3TC = lamivudine, ABC = abacavir, ARV = antiretroviral, ATV = atazanavir, d4T = stavudine, ddI = didanosine, DRV = darunavir, EFV = efavirenz, ETR = etravirine, EVG = elvitegravir, FPV = fosamprenavir, FTC = emtricitabine, IDV = indinavir, LPV/r = lopinavir/ritonavir, MVC = maraviroc, NFV = nelfinavir, NNRTI = non-nucleoside reverse transcriptase inhibitor, NRTI = nucleoside reverse transcriptase inhibitor, NVP = nevirapine, PI = protease inhibitor, RAL = raltegravir, RTV = ritonavir, SQV = saquinavir, T-20 = enfuvirtide, TDF = tenofovir, RPV = rilpivirine, TPV = tipranavir, ZDV = zidovudine

Table 9. ARV Regimens or Components that Should Never Be Recommended for Treatment of HIV Infection in Children

	Rationale	Exceptions
ARV regimens never recommended for children		
One ARV drug alone (monotherapy)	• Rapid development of resistance • Inferior antiviral activity compared with combination including ≥3 ARV drugs	• HIV-exposed infants (with negative viral testing) during 6-week period of prophylaxis to prevent perinatal transmission of HIV • 3TC or FTC interim "bridging regimen" in special circumstances of children with treatment failure associated with drug resistance and persistent nonadherence
Two NRTIs alone	• Rapid development of resistance • Inferior antiviral activity compared with combination including ≥3 ARV drugs	• Not recommended for initial therapy • For patients currently on 2 NRTIs alone who achieve virologic goals, some clinicians may opt to continue this treatment.
TDF ***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 exceptions
TDF ***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 exceptions
ARV components never recommended as part of an ARV regimen for children		
ATV ***plus*** IDV	• Potential additive hyperbilirubinemia	• No exceptions
Dual-NNRTI combinations	• Enhanced toxicity	• No exceptions
Dual-NRTI combinations: • 3TC ***plus*** FTC • d4T ***plus*** ZDV	• Similar resistance profile and no additive benefit • Antagonistic effect on HIV	• No exceptions • No exceptions
EFV in first trimester of pregnancy or for sexually active adolescent girls of childbearing potential when reliable contraception cannot be ensured	• Potential for teratogenicity	• When no other ARV option is available and potential benefits outweigh risks
NVP in adolescent girls with CD4 count >250 cells/mm^3 or adolescent boys with CD4 count >400 cells/mm^3	• Increased incidence of symptomatic (including serious and potentially fatal) hepatic events in these patient groups	• Only if benefit clearly outweighs risk
Unboosted SQV, DRV, or TPV	• Poor oral bioavailablity • Inferior virologic activity compared with other PIs	• No exceptions

Key to Abbreviations: 3TC = lamivudine, ABC = abacavir, ARV = antiretroviral, ATV = atazanavir, d4T = stavudine, ddI = didanosine, DRV = darunavir, EFV = efavirenz, FTC = emtricitabine, IDV = indinavir, NNRTI = non-nucleoside reverse transcriptase inhibitor, NRTI = nucleoside reverse transcriptase inhibitor, NVP = nevirapine, PI = protease inhibitor, SQV = saquinavir, TDF = tenofovir, TPV = tipranavir, ZDV = zidovudine

Table 10. Advantages and Disadvantages of Different NRTI Backbone Combinations for Use in Combination ARV Regimens for Initial Therapy in Children (page 1 of 2) (see Pediatric Antiretroviral Drug Information Appendix for more information)

	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.	• Risk of ABC HSR; perform HLA-B*5701 screening before initiation of ABC treatment.
ZDV ***plus*** (3TC ***or*** FTC)	• Extensive pediatric experience • ZDV and 3TC are coformulated as single pill for older/larger patients. • Palatable liquid formulations • Can give with food • FTC is available as a palatable liquid formulation administered once daily.	• Bone marrow suppression with ZDV • Lipoatrophy with ZDV
TDF ***plus*** (3TC ***or*** FTC) for adolescents, Tanner Stage 4 or 5	• Resistance slow to develop • Once-daily dosing for TDF • Less mitochondrial toxicity than other NRTIs • Can give with food • Bone toxicity may be less in postpubertal children. • TDF and FTC are coformulated as single pill for older/larger patients.	• Limited pediatric experience • Potential bone and renal toxicity • Appropriate dosing is complicated by numerous drug-drug interactions with other ARV agents including ddI, LPV/r, ATV, and TPV.
Alternative Combinations		
ddI ***plus*** (3TC ***or*** 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 adherence is an issue (ddI can be coadministered with FTC or 3TC). • Limited pediatric experience using delayed-release ddI capsules in younger children • Pancreatitis, neurotoxicity with ddI
TDF ***plus*** (3TC ***or*** FTC) for adolescents, Tanner Stage 3	• Resistance slow to develop • Once-daily dosing for TDF • Less mitochondrial toxicity than other NRTIs • Can give with food • TDF and FTC are coformulated as single pill for older/larger patients. • Available as reduced-strength tablets and oral powder for use in younger children	• Limited pediatric experience • Potential for bone and renal toxicity • Numerous drug-drug interactions with other ARV agents including ddI, LPV/r, ATV, and TPV complicate appropriate dosing.

Table 10. Advantages and Disadvantages of Different NRTI Backbone Combinations for Use in Combination ARV Regimens for Initial Therapy in Children (page 2 of 2) (see Pediatric Antiretroviral Drug Information Appendix for more information)

	Advantages	Disadvantages
Alternative Combinations, continued		
ZDV ***plus*** ABC	• Palatable liquid formulations • Can give with food	• Risk of ABC HSR; perform HLA-B*5701 screening before initiation of ABC treatment. • Bone marrow suppression and lipoatrophy 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 doses.	• Bone marrow suppression and lipoatrophy with ZDV • Pancreatitis, neurotoxicity with ddI • ddI liquid formulation is 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 adherence is an issue.
Use in Special Circumstances		
d4T ***plus*** (3TC ***or*** FTC)	• Extensive pediatric experience • Palatable liquid formulations • Can give with food • FTC is 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
TDF ***plus*** (3TC ***or*** FTC) for children, Tanner Stage 1 or 2	• Resistance slow to develop • Once-daily dosing for TDF • Less mitochondrial toxicity than other NRTIs • Can give with food • Bone toxicity may be less in postpubertal children. • TDF and FTC are coformulated as single pill for older/larger patients. • Available as reduced strength tablets and oral powder for use in younger children	• Limited pediatric experience • Potential bone and renal toxicity • Numerous drug-drug interactions with other ARV agents including ddI, LPV/r, ATV, and TPV complicate appropriate dosing.
Not Recommended		
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 can be considered for use in ARV-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
ZDV ***plus*** d4T	• None	• Pharmacologic and antiviral antagonism

Key to Abbreviations: 3TC = lamivudine, ABC = abacavir, ARV = antiretroviral, ATV = atazanavir, d4T = stavudine, ddI = didanosine, FTC = emtricitabine, HSR = hypersensitivity reaction, LPV/r = lopinavir/ritonavir, NRTI = nucleoside reverse transcriptase inhibitor, PK = pharmacokinetic, TDF = tenofovir, TPV = tipranavir, ZDV = zidovudine

Table 11. Advantages and Disadvantages of Different NNRTIs for Use in Combination ARV Regimens for Initial Therapy in Children (page 1 of 2) (see Pediatric Antiretroviral Drug Information Appendix for more information)

	Advantages	Disadvantages
General Issues		
NNRTI-based Regimens	**NNRTI Class Advantages:** • Less dyslipidemia and fat maldistribution than PIs • PI sparing • Lower pill burden than PIs for children taking solid formulation; easier to use and adhere to than PI-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 SJS, 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		
EFV (for children aged ≥3 years who can take capsules)	• Potent ARV activity • Once-daily administration • Can give with food (but avoid high-fat meals)	• Neuropsychiatric adverse effects (bedtime dosing recommended to reduce CNS effects) • Rash (generally mild) • No commercially available liquid • No data on dosing for children aged <3 years • Teratogenic in primates; use with caution in adolescent females of childbearing age.
Alternative		
NVP	• Liquid formulation available • Dosing information for young infants available • Can give with food	• Reduced virologic efficacy in young infants, regardless of exposure to NVP as part of a PMTCT regimen • Higher incidence of rash/HSR than other NNRTIs • Higher rates of serious hepatic toxicity than EFV • Decreased virologic response compared with EFV • Need to initiate therapy with a lower dose and increase in a stepwise fashion. This is to allow for auto-induction of NVP metabolism and is associated with a lower incidence of toxicity. • Twice-daily dosing
Not Recommended		
EFV (for children aged <3 years)	• Potent ARV activity • Once-daily administration • Can give with food (but avoid high-fat meals)	• Neuropsychiatric adverse effects (bedtime dosing recommended to reduce CNS effects) • Rash (generally mild) • No commercially available liquid • No data on dosing for children aged <3 years • Teratogenic in primates; use with caution in adolescent females of childbearing age.

Table 11. Advantages and Disadvantages of Different NNRTIs for Use in Combination ARV Regimens for Initial Therapy in Children (page 2 of 2) (see Pediatric Antiretroviral Drug Information Appendix for more information)

	Advantages	Disadvantages
Not Recommended, continued		
ETR	• 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 ETR-related rash.	• Limited data on pediatric dosing or safety • No pediatric formulation available • Food effect (should be given with food) • No data in treatment-naive patients • Multiple drug interactions with PIs and other medications • Twice-daily dosing • Skin rash
RPV	• Once-daily administration • Reduced CNS effects compared with EFV • Not associated with embryofetal abnormalitites	• No data on pediatric dosing or safety • No pediatric formulation available • Compared with EFV, has higher rate of treatment failure and cross resistance to the NNRTI class in adults • Adults with viral loads >100,000 copies/mL are more likely to experience virologic failure than are patients with viral loads <100,000 copies/mL.

Key to Abbreviations: ARV = antiretroviral, CNS = central nervous system, CYP3A4 = cytochrome P450, EFV = efavirenz, ETR = etravirine, HSR = hypersensitivity reaction, NNRTI = non-nucleoside reverse transcriptase inhibitor, NVP = nevirapine, PI = protease inhibitor, PMTCT = prevention of mother-to-child transmission, SJS = Stevens-Johnson syndrome, RPV= rilpivirine

Table 12. Advantages and Disadvantages of Different PIs for Use in Combination ARV Regimens for Initial Therapy in Children (page 1 of 4) (see Pediatric Antiretroviral Drug Information Appendix for more information)

	Advantages	Disadvantages
General Issues		
PI-based Regimens	**PI Class Advantages:** • NNRTI sparing • Clinical, virologic, and immunologic efficacy well documented • Resistance to PIs requires multiple mutations • Targets HIV at 2 steps of viral replication (viral reverse transcriptase and protease enzymes)	**PI Class Disadvantages:** • Metabolic complications including dyslipidemia, fat maldistribution, insulin resistance • Potential for multiple drug interactions because of metabolism via hepatic enzymes (e.g., CYP3A4) • Higher pill burden than NRTI- or NNRTI-based regimens for patients taking solid formulations • Poor palatability of liquid preparations, which may affect adherence to treatment regimen
Preferred		
ATV in combination with low-dose RTV in children aged ≥6 years	• Once-daily dosing • ATV has less effect on TG and total cholesterol levels than other PIs (but RTV boosting may be associated with elevations in these parameters).	• No liquid formulation • Food effect (should be administered with food) • Indirect hyperbilirubinemia common but asymptomatic • Must be used with caution in patients with pre-existing conduction system defects (can prolong PR interval of ECG)
LPV/r	• Coformulated liquid and tablet formulations • Tablets can be given without regard to food but may be better tolerated when taken with meal or snack.	• Poor palatability of liquid formulation (bitter taste), although palatability of combination better than RTV alone • Food effect (liquid formulation should be administered with food) • RTV component associated with large number of drug interactions (see RTV) • Should not be administered to neonates before a postmenstrual age (first day of the mother's last menstrual period to birth plus the time elapsed after birth) of 42 weeks and a postnatal age of at least 14 days • Must be used with caution in patients with pre-existing conduction system defects (can prolong PR and QT interval of ECG)
Alternative		
DRV in combination with low-dose RTV in children aged ≥3 years	• Effective in PI-experienced children when given with low-dose RTV boosting	• Pediatric pill burden high with current tablet dose formulations • No liquid formulation • Food effect (should be given with food) • Must be given with RTV boosting to achieve adequate plasma concentrations • Contains sulfa moiety. The potential for cross sensitivity between DRV and other drugs in sulfonamide class is unknown. • Cannot administer once daily in children aged <12 years

Table 12. Advantages and Disadvantages of Different PIs for Use in Combination ARV Regimens for Initial Therapy in Children (page 2 of 4) (see Pediatric Antiretroviral Drug Information Appendix for more information)

	Advantages	Disadvantages
FPV in combination with low-dose RTV in children aged ≥6 months	• Oral prodrug of APV with lower pill burden • Pediatric formulation available, which should be given to children with food	• Skin rash • More limited pediatric experience than preferred PI • Must be given with food to children • RTV component associated with large number of drug interactions (see RTV) • Contains sulfa moiety. Potential for cross sensitivity between FPV and other drugs in sulfonamide class is unknown. • Should only be administered to infants born at ≥38 weeks' gestation and who have attained a postnatal age of 28 days
Use in Special Circumstances		
ATV (unboosted) in treatment-naive adolescents aged ≥13 years and weight >39 kg who are unable to tolerate RTV	• Once-daily dosing • Less effect on TG and total cholesterol levels than other PIs	• No liquid formulation • Food effect (should be administered with food) • Indirect hyperbilirubinemia common but asymptomatic • Must be used with caution in patients with pre-existing conduction system defects (can prolong PR interval of ECG) • May require RTV boosting in treatment-naive adolescent patients to achieve adequate plasma concentrations • Unboosted ATV cannot be used with TDF
FPV (unboosted) in children aged ≥2 years	• Oral prodrug of APV with lower pill burden • Pediatric formulation available • Can give with food	• Skin rash • More limited pediatric experience than preferred PI • May require boosted regimen to achieve adequate plasma concentrations; PK data to define appropriate dosing not yet available.
NFV in children aged ≥2 years	• Can give with food • Simplified 2-tablet (625 mg) twice-daily regimen has a reduced pill burden compared with other PI-containing regimens in older patients where the adult dose is appropriate.	• Diarrhea • 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 • Less potent than boosted PIs

Table 12. Advantages and Disadvantages of Different PIs for Use in Combination ARV Regimens for Initial Therapy in Children (page 3 of 4) (see Pediatric Antiretroviral Drug Information Appendix for more information

	Advantages	Disadvantages
Not Recommended		
ATV (unboosted) in children aged <13 years and/or weight <39 kg	• Once-daily dosing (aged >13 years) • Less effect on TG and total cholesterol levels than other PIs	• Drug levels low if used without RTV boosting • No liquid formulation • Food effect (should be administered with food) • Indirect hyperbilirubinemia common but asymptomatic • Must be used in caution in patients with pre-existing conduction system defects (can prolong PR interval of ECG) • May require RTV boosting in treatment-naive adolescent patients to achieve adequate plasma concentrations
IDV (unboosted or boosted)	• Can be considered for use as component of a regimen in combination with low-dose RTV 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 PK data
NFV in children aged <2 years	• Can give with food	• Diarrhea • 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 • Less potent than boosted PIs
RTV (full dose as single PI)	• Liquid formulation • Can give with food	• Poor palatability of liquid (bitter taste) • GI intolerance • Food effect (should be administered with food) • Large number of drug interactions (most potent inhibitor of CYP3A4)
SQV (unboosted or boosted)		• Low bioavailability, should never be used as sole PI • Limited pediatric PK data; will require boosting with another PI (e.g., RTV) to achieve adequate concentrations. • No liquid formulation • High pill burden • Must be taken with food • Potential for photosensitivity reactions

Table 12. Advantages and Disadvantages of Different PIs for Use in Combination ARV Regimens for Initial Therapy in Children (page 4 of 4) (see Pediatric Antiretroviral Drug Information Appendix for more information)

	Advantages	Disadvantages
TPV	• Effective in PI-experienced children and adults when given with low-dose RTV boosting • Liquid formulation	• Limited data in treatment-naive patients • Food effect (should be administered with food) • Must be given with RTV boosting to achieve adequate plasma concentrations

Key to Abbreviations: APV = amprenavir, ARV = antiretroviral, ATV = atazanavir, CYP3A4 = cytochrome P450, DRV = darunavir, ECG = electrocardiogram, FPV = fosamprenavir, GI = gastrointestinal, IDV = indinavir, LPV/r = lopinavir/ritonavir, NFV = nelfinavir, NNRTI = non-nucleoside reverse transcriptase inhibitor, NRTI = nucleoside reverse transcriptase inhibitor, PI = protease inhibitor, PK = pharmacokinetic, RTV = ritonavir, SQV = saquinavir, TDF = tenofovir, TG = triglyceride, TPV = tipranavir

Table 13. Advantages and Disadvantages of Entry Inhibitors for Use in Combination ARV Regimens (see Pediatric Antiretroviral Drug Information Appendix for more information)

	Advantages	Disadvantages
General Issues		
Entry Inhibitors	**Entry Inhibitor Class Advantages:** • Susceptibility of HIV to a new class of ARVs	**Entry Inhibitor Class Disadvantages:** • Rapid development of resistance with T-20 • CCR5 inhibitors are ineffective against CXCR4 virus, mixed CCR5 and CXCR4 viral populations, or dual-tropic virus.
Use in Special Circumstances		
T-20	• Susceptibility of HIV to a new class of ARVs • Route of administration ensures adequate drug levels	• Twice-daily subcutaneous injections • 98%–100% incidence of local injection site reactions • Poor adherence and limited levels of success in adolescents because of local site reactions
Insufficient Data to Recommend		
MVC	• Susceptibility of HIV to a new class of ARVs • Can give with food	• Ineffective against CXCR4 or mixed/dual-tropic viral populations • Limited data on pediatric dosing or safety • No pediatric formulation • Multiple drug interactions; different dosing depending on NNRTI or PI coadministered with MVC.

Key to Abbreviations: ARV = antiretroviral, MVC = maraviroc, NNRTI = non-nucleoside reverse transcriptase inhibitor, PI = protease inhibitor, T-20 = enfuvirtide

Table 14. Advantages and Disadvantages of Integrase Inhibitors for Use in Combination ARV Regimens

	Advantages	Disadvantages
General Issues		
Integrase Inhibitors	**Integrase Inhibitor Class Advantages:** • Susceptibility of HIV to a new class of ARVs	**Integrase Inhibitor Class Disadvantages:** • Limited data on pediatric dosing or safety
Insufficient Data to Recommend		
EVG only available as a coformulated product containing EVG/COBI/FTC/TDF	• One tablet, once daily • The single tablet is a complete combination regimen in antiretroviral-naive patients.	• No data on use in patients aged <18 years • Potential bone and renal toxicity • Potential for many drug interactions from cobicistat (COBI), a CYP3A4 inhibitor with pharmacokinetic actions similar to RTV • Must be taken with food
RAL	• Susceptibility of HIV to a new class of ARVs • Can give with food • Available in a chewable tablet	• Limited data on pediatric dosing or safety • Potential for rare systemic allergic reaction or hepatitis

Key to Abbreviations: ARV = antiretroviral, COBI = cobicistat, EVG = elvitegravir, FTC = emtricitabine, RAL = raltegravir, RTV= ritonavir, TDF = tenofovir disoproxil fumarate

Table 15. Sample Schedule for Clinical and Laboratory Monitoring of Children Before and After Initiation of Antiretroviral Therapy (page 1 of 2)

	Entry Into Care	Monitoring Pre-Therapy[1]	ART Initiation[1]	1–2 Weeks on Therapy[2]	4–8 Weeks on Therapy	Every 3–4 Months[3]	Every 6–12 Months	ARV Switch
Clinical History Physical Exam[2]	X	X	X	X	X	X	X	X
CBC w/ Differential	X	X	X		X	X		X
Chemistries[4]	X		X		X[4]	X		X
Electrolytes	X		X			X		X
Glucose	X		X			X		X
AST/ALT	X	X	X	X[5]	X[5]	X		X
Bilirubin	X		X			X		X
BUN/Creatinine	X	X	X			X		X
Albumin/Total Protein	X		X				X	X
Ca/Phosphate	X		X				X	X
CD4 Count/%	X	X	X		X[6]	X		X
HIV RNA	X	X	X	X[2]	X	X		X

Table 15. Sample Schedule for Clinical and Laboratory Monitoring of Children Before and After Initiation of Antiretroviral Therapy (page 2 of 2)

	Entry Into Care	Monitoring Pre-Therapy[1]	ART Initiation[1]	1–2 Weeks on Therapy[2]	4–8 Weeks on Therapy	Every 3–4 Months[3]	Every 6–12 Months	ARV Switch
Resistance Testing	X							X
Adherence Evaluation			X	X	X	X		X
Lipid Panel	X		X				X	
Urinalysis	X		X				X	

[1] When therapy is started within 30 to 45 days of a Monitoring Pre-Therapy lab result, repeat testing may not be necessary.

[2] Children starting a new ARV regimen should be evaluated in person or by phone within 1 to 2 weeks of starting medication to screen for clinical side effects and to ensure that they are adhering to the regimen. Many clinicians will plan additional contacts (in person or by telephone) with children and caregivers to support adherence during the first few weeks of therapy. Some clinicians also recommend an HIV RNA measurement within the initial weeks of therapy for early assessment of response/adherence to therapy.

[3] For children who are in a stable treatment status (non-detectable HIV RNA and normal CD4 count/percentage for at least 12 months) many clinicians are considering 6-month intervals between monitoring lab tests. Some clinicians find value in visits every 3 months even when lab testing is not performed (such as to review adherence and update dosing for interim growth).

[4] Some ARV drugs, such as nevirapine and tenofovir, require a specific schedule frequency based on toxicity profile (see specific antiretroviral agents).

[5] In children receiving nevirapine, serum transaminase levels should be measured every 2 weeks for the first 4 weeks of therapy, then monthly for 3 months, and every 3 to 4 months thereafter.

[6] Some clinicians do not recommend a CD4 cell count/percentage at this time, considering it too early to expect an immunologic response.

Key to Abbreviations: ARV = antiretroviral, CBC = complete blood count, AST = aspartate aminotransferase, ALT = alanine aminotransferase, BUN = blood urea nitrogen

Table 16. Strategies to Improve Adherence to Antiretroviral Medications

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, substance abuse, or other mental health issues for the child/adolescent and/or caregiver that may decrease adherence. Treat mental health issues before starting antiretroviral (ARV) drugs, if possible.
• Identify family, friends, health team members, or others who can support adherence.
• 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 ARV drug (that is, 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.
• Assess pill-swallowing capacity and offer pill-swallowing training.
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 associated with demands to attain 95% adherence with medication doses.
• Use patient education aids including pictures, calendars, and stickers.
• Encourage use of pill boxes, reminders, alarms, pagers, and timers.
• Provide follow-up clinic visits, telephone calls, and text messages to support and assess adherence.
• 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, such as medication education and counseling, refill reminders, and home delivery of medications.
• Consider gastrostomy tube use in selected circumstances.
• Consider directly observed therapy (DOT) at home, in the clinic, or during a brief inpatient hospitalization.

Table 17a. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Central Nervous System (CNS) Toxicity (Last updated November 1, 2012; last reviewed November 1, 2012) (page 1 of 2)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention / Monitoring	Management
Global CNS depression	LPV/r oral solution (contains both ethanol and propylene glycol as excipients)	Onset: 1–6 days after starting LPV/r Presentation: Neonates/preterm infants: global CNS depression, cardiac toxicity, respiratory complications	Exact frequency unknown, but ethanol and propylene glycol toxicity at therapeutic LPV/r dose reported in premature neonates	Prematurity Low birth weight Age <14 days (whether premature or term)	Avoid use of LPV/r until a postmenstrual age of 42 weeks and a postnatal age of at least 14 days.	Discontinue LPV/r; symptoms should resolve in 1–5 days. If needed, reintroduction of LPV/r can be considered once outside the vulnerable period.
Neuropsychiatric symptoms and other CNS manifestations	EFV	Onset: 1–2 days after initiating treatment Most symptoms subside or diminish by 2–4 weeks (but may persist in a minority of patients) Presentation: May include one or more of the following: dizziness, somnolence, insomnia, abnormal dreams, impaired concentration, psychosis, suicidal ideation, seizures (including absence seizures) CNS side effects may be more difficult to detect in children because neurologic symptoms such as impaired concentration, sleep disturbances, or behavior disorders may be difficult to assess.	Variable, depending on age, symptom, assessment method Children: 24% for any EFV-related CNS manifestations in one case series with 18% requiring drug discontinuation Adults: >50% for any CNS manifestations of any severity 2% for EFV-related severe CNS manifestations	Insomnia associated with elevated EFV trough concentration ≥4 mcg/mL Presence of CYP450 polymorphisms that decrease EFV metabolism (CYP2B6 516 TT genotype) Prior history of psychiatric illness or use of psychoactive drugs	Administer EFV on an empty stomach, preferably at bedtime. TDM can be considered in the context of a child with mild or moderate toxicity possibly attributable to a particular ARV agent (see Role of Therapeutic Drug Monitoring in Management of Treatment Failure).	Provide reassurance about the likely time-limited nature of symptoms. Consider EFV trough level if symptoms excessive or persistent. If EFV trough level >4 mcg/mL, consider dose reduction, preferably with expert pharmacologist input or drug discontinuation.

Table 17a. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Central Nervous System (CNS) Toxicity (Last updated November 1, 2012; last reviewed November 1, 2012) (page 2 of 2)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention / Monitoring	Management
	RAL	Presentation: Increased psychomotor activity, headaches, insomnia, depression	Children: Psychomotor activity reported in one child Adults: Headache, insomnia (<5% in adult trials)	Elevated RAL concentrations Prior history of insomnia or depression	Use with caution in the presence of drugs that increase RAL concentration	Consider drug discontinuation in case of severe insomnia.
Intracranial hemorrage	TPV	Onset: 7–513 days after starting TPV	Children: No cases of ICH reported in children Adults: In premarket approval data in adults, 0.23/100 patient-years or 0.04–0.22/100 patient-years in a retrospective review of 2 large patient databases	Unknown; prior history of bleeding disorder or risk factors for bleeding present in most patients in case series reported	Administer TPV with caution in patients with bleeding disorder, known intracranial lesions, recent neurosurgery.	Discontinue TPV if ICH is suspected or confirmed.
Cerebellar ataxia	RAL	Onset: As early as 3 days after starting RAL Presentation: Tremor, dysmetria, ataxia	Two cases reported in adults during post marketing period	Unknown; a speculated mechanism may include recent treatment with ATV with residual UGT1A1 enzyme inhibition and increased RAL serum concentration	Use with caution with ATV or other drugs that cause strong inhibition of UGT1A1 enzyme	Consider drug discontinuation. RAL reintroduction can be considered if predisposing factor (such as drug-drug interaction) identified and removed.

Key to Acronyms: ARV = antiretroviral, CNS = central nervous system, CYP = cytochrome P, EFV = efavirenz, ICH = intracranial hemorrhage, LPV/r = lopinavir/ritonavir, RAL = raltegravir, TDM = therapeutic drug monitoring, UGT = uridine diphosphate-glucurononyl transferase, TPV = tipranavir, ATV = atazanavir

Table 17b. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Dyslipidemia (page 1 of 2) (Last updated November 1, 2012; last reviewed November 1, 2012)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention / Monitoring	Management
Dyslipidemia	PIs: All PIs; lower incidence with ATV and DRV NRTIs: Especially d4T NNRTIs: RPV < EFV	Onset: Weeks to months after beginning therapy Presentation: *PIs:* ↑LDL-C, TC, and TG *NNRTIs:* ↑LDL-C, TC, and HDL-C *NRTIs:* ↑LDL-C, TC, and TG	20%–50% of children receiving ART will have lipoprotein abnormalities.	HIV infection High-fat, high-cholesterol diet Lack of exercise Obesity Hypertension Smoking Family history of dyslipidemia or premature CVD Metabolic syndrome	Prevention: Low-fat diet, exercise, no smoking Monitoring: *Adolescents and adults:* Obtain fasting (12-hour) TC, HDL-C, non-HDL-C, LDL-C, and TG before initiating or changing ART, then every 6 months, and thereafter, every 6–12 months. *Children (aged ≥2 years) without lipid abnormalities or additional risk factors:* Obtain non-fasting screening lipid profiles before initiating or changing therapy and then, if levels are stable, every 6–12 months. If TG or LDL-C is elevated, obtain fasting blood tests. *Children with lipid abnormalities and/or additional risk factors:* Obtain fasting (12-hour) TC, HDL-C, TG, and LDL-C before initiating or changing therapy and every 6 months thereafter (or more often if indicated). *Children receiving lipid-lowering therapy with statins or fibrates:* Obtain fasting (12-hour) lipid profiles, LFTs, and CK before initiating lipid therapy and at 4 weeks and 8 weeks after starting lipid therapy. If minimal alterations in AST, ALT, and CK, repeat tests every 3 months. Also repeat tests 4 weeks after increasing doses of antihyperlipidemic agents.	Counsel lifestyle modification (low-fat diet, exercise, smoking cessation) for adequate trial period (3–6 months). Switch to a new ART regimen less likely to cause lipid abnormalities.[a] Pharmacologic Management: Initiate drug therapy promptly in patients with TG ≥500 mg/dL: Statins such as pravastatin, atorvastatin, or rosuvastatin.[b] Ezetimibe may be considered in addition to statins.[c] Fibrates (gemfibrozil and fenofibrate) and N-3 PUFAs derived from fish oils may be used as alternative agents for adults with ↑TG but are not approved for use in children. No consensus as to what LDL-C should prompt treatment in children receiving ARVs.[d] HIV-infected patients are considered to be at moderate risk of CVD. Assessment of additional risk factors should be done in all patients.[e] *High-risk patients:* Goal LDL-C ≤100 mg/dL. *Moderate-risk patients:* Goal LDL-C ≤130 mg/dL. *At-risk patients:* Goal LDL-C ≤160 mg/dL.

Table 17b. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Dyslipidemia (page 2 of 2) (Last updated November 1, 2012; last reviewed November 1, 2012)

[a] The risks of new treatment-related toxicities and virologic failure that could occur with changes in therapy must be weighed against the potential risk of drug interactions and toxicities associated with the use of lipid-lowering agents.

[b] Statins (HMG-CoA reductase inhibitors) are contraindicated in pregnancy (potentially teratogenic) and should not be used in patients who may become pregnant. Serious toxicities include hepatotoxicity, skeletal muscle toxicity, and rhabdomyolysis. Experience with statins is limited to children >6 years of age.

[c] In general, recommend using in boys aged ≥10 years and in girls preferably after onset of menses. Treatment with statins in children ≤10 years of age is limited to those with severe primary hyperlipidemia, a high-risk condition, or evident CVD, all under the care of a lipid specialist. Multiple drug interactions exist between ARVs and statins (exception pravastatin, which is not dependent on CYP3A4 for metabolism). Pravastatin (Pravachol®), atorvastatin (Lipitor®), rosuvastatin (Crestor®), fluvastatin (Lescol®), and ezetimide (Zetia®) are approved for use in children ≥10 years of age.

[d] The long-term risks of lipid abnormalities in children receiving ART are unclear. However, persistent dyslipidemia in children is likely to lead to premature CVD.

[e] Refer to NHLBI guidelines at http://www.nhlbi.nih.gov/guidelines/cvd_ped/summary.htm#chap9.

Key to Acronyms: ALT = alanine transaminase, ARV = antiretroviral, AST = aspartate aminotransferase, ATV = atazanavir, ART = antiretroviral therapy, CK = creatine kinase, CVD = cardiovascular disease, d4T = stavudine, EFV = efavirenz, HDL-C = high-density lipoprotein cholesterol, non-HDL-C= non-high-density lipoprotein cholesterol, LDL-C = low density lipoprotein cholesterol, LFT = liver function tests, NNRTI = non-nucleoside reverse transcriptase inhibitor, NRTI = nucleoside reverse transcriptase inhibitor, PI = protease inhibitor, PUFA = polyunsaturated fatty acid, RPV = rilpivirine, TC = total cholesterol, TG = triglycerides

Table 17c. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Gastrointestinal Effects (Last updated November 1, 2012; last reviewed November 1, 2012)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention / Monitoring	Management
Nausea/ Vomiting	Principally ZDV and PIs (such as LPV/r, RTV) but can occur with all ARVs	Onset: Early Presentation: Nausea, emesis—may be associated with anorexia and/or abdominal pain	Varies with ARV agent. 10%–30% in some series.	Unknown	Instruct patient to take PIs with food. Generally improves with time; monitor for weight loss, ARV adherence.	Reassure patient/ caretaker that nausea and vomiting will likely decrease over time. Provide supportive care including instruction on dietary modification. Although antiemetics are not generally indicated, they may be useful in extreme or persistent cases.
Diarrhea	PIs (NFV, LPV/r, FPV/r), buffered ddI	Onset: Early Presentation: Generally soft, more frequent stools	Varies with ARV agent. 10%–30% in some series.	Unknown	Generally improves with time (usually over 6–8 weeks); monitor for weight loss, dehydration.	Exclude infectious causes of diarrhea. Although data in children on treatment for ARV-associated diarrhea are lacking, dietary modification, use of calcium carbonate, bulk-forming agents (psyllium), or antimotility agents (loperamide) may be helpful.
Pancreatitis	ddI (especially with concurrent d4T or TDF); reported, albeit rarely, with most ARVs	Onset: Any time, usually after months on therapy Presentation: Emesis, abdominal pain, elevated amylase and lipase (asymptomatic hyperamylasemia or elevated lipase do not in and of themselves indicate pancreatitis)	<1%–2% in recent series. Frequency was higher in the past with higher dosing of ddI.	Concomitant treatment with other medications associated with pancreatitis (such as TMP-SMX, pentamidine, ribavirin) Hypertriglyceridemia	Avoid use of ddI in patients with history of pancreatitis.	Discontinue offending agent. Manage symptoms of acute episode. If associated with hypertriglyceridemia, consider interventions to lower TG levels.

Key to Acronyms: ARV = antiretroviral, d4T = stavudine, ddI = didanosine, FPV/r = fosamprenavir/ritonavir, LPV = lopinavir, LPV/r = lopinavir/ritonavir, NFV = nelfinavir, PI = protease inhibitor, RTV = ritonavir, TDF = tenofovir disoproxil fumarate, TG = triglyceride, TMP-SMX = trimethoprim sulfamethoxazole, ZDV = zidovudine

Table 17d. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Hematologic Effects (Last updated November 1, 2012; last reviewed November 1, 2012) (page 1 of 2)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention / Monitoring	Management
Anemia[a]	Principally ZDV	Onset: Variable, weeks to months Presentation: Most commonly asymptomatic or mild fatigue, pallor, tachypnea; rarely, congestive heart failure	HIV-exposed newborns: Severe anemia uncommon, but may be seen coincident with physiologic Hgb nadir HIV-infected children on ARVs: 2–3 times more common with ZDV-containing regimens; less frequent with currently recommended dosing of ZDV	HIV-exposed newborns: Premature birth *In utero* exposure to ARVs Advanced maternal HIV Neonatal blood loss Concurrent ZDV + 3TC neonatal prophylaxis HIV-infected children on ARVs: Underlying hemoglobinopathy (sickle cell disease, G6PD deficiency) Myelosuppressive drugs (e.g., TMP-SMX, rifabutin) Iron deficiency Advanced or poorly controlled HIV disease	HIV-exposed newborns: Monitor CBC at birth. Consider repeat CBC at 4 weeks for neonates who are at higher risk (such as those born prematurely or known to have low birth Hgb). HIV-infected children on ARVs: Avoid ZDV in children with moderate to severe anemia when alternative agents are available. Monitor CBC 3–4 times per year as part of routine care.	HIV-exposed newborns: Rarely require intervention unless Hgb is <7.0 g/dL or anemia is associated with symptoms. Consider discontinuing ZDV if 4 weeks or more of 6-week ZDV prophylaxis regimen are already completed (see Perinatal Guidelines[b]). HIV-infected children on ARVs: Discontinue non-ARV marrow-toxic drugs, if feasible. Treat coexisting iron deficiency, OIs, malignancies. For persistent severe anemia thought to be associated with ARVs, change to a non-ZDV-containing regimen; consider a trial of erythropoietin.

Table 17d. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Hematologic Effects (Last updated November 1, 2012; last reviewed November 1, 2012) (page 2 of 2)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention / Monitoring	Management
Neutropenia[a]	Principally ZDV	Onset: Variable Presentation: Most commonly asymptomatic	HIV-exposed newborns: Rare HIV-infected children on ARVs: 9.9%–26.8% of children on ARVs, depending upon the ARV regimen Highest rates with ZDV-containing regimens	HIV-exposed newborns: *In utero* exposure to ARVs Concurrent ZDV + 3TC neonatal prophylaxis HIV-infected children on ARVs: Advanced or poorly controlled HIV infection Myelosuppressive drugs (such as TMP-SMX, ganciclovir, hydroxyurea, rifabutin)	HIV-infected children on ARVs: Monitor CBC 3–4 times per year as part of routine care.	HIV-exposed newborns: No established threshold for intervention; some experts would consider using an alternative NRTI for prophylaxis if ANC <500 cells/μL, or discontinue ARV prophylaxis entirely if ≥4 weeks of 6-week ZDV prophylaxis have been completed (see Perinatal Guidelines[b]). HIV-infected children on ARVs: Discontinue non-ARV marrow-toxic drugs if feasible. Treat coexisting OIs, malignancies. For persistent severe neutropenia thought to be associated with ARVs, change to a non-ZDV-containing regimen; consider a trial of G-CSF.

[a] HIV infection itself, OIs, and medications used to prevent OIs, such as TMP-SMX, may all contribute to anemia, neutropenia, and thrombocytopenia.

[b] *Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States*

Key to Acronyms: 3TC = lamivudine, ANC = absolute neutrophil count, ARV = antiretroviral, CBC = complete blood count, G6PD = glucose-6-phosphate dehydrogenase, G-CSF = granulocyte colony-stimulating factor, Hgb = hemoglobin, NRTI = nucleoside reverse transcriptase inhibitor, OIs = opportunistic infections, TMP-SMX = trimethoprim-sulfamethoxazole, ZDV = zidovudine

Table 17e. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Hepatic Events (Last updated November 1, 2012; last reviewed November 1, 2012) (page 1 of 2)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention / Monitoring	Management
Hepatic toxicity (elevated AST, ALT, clinical hepatitis)	All ARVs (NVP, TPV of particular concern)	Onset: *NNRTI and PI therapy:* Within 12 weeks of initiation. *NRTI therapy:* Within months to years of initiation. *Any ARV combination regimen:* Early due to IRIS. Presentation: Asymptomatic elevation of AST, ALT. May be associated with symptoms of clinical hepatitis including nausea, fatigue, and jaundice. AST, ALT elevations while on NVP, ABC, or RAL may be associated with skin rash or a hypersensitivity reaction. HBV-coinfected patients may develop severe hepatic flare with initiation, withdrawal, or when resistance develops with 3TC, FTC, and TDF. NRTIs, especially ZDV, ddI, and d4T, may be associated with lactic acidosis and hepatic steatosis.	Uncommon in children. Frequency varies with different agents and drug combinations.	HIV infection HBV or HCV coinfection Elevated baseline ALT, AST Other hepatotoxic medications Alcohol use Underlying liver disease Pregnancy For NVP-associated hepatic events in adults: Female with pre-NVP CD4 count >250 cells/mm^3 Male with pre-NVP CD4 count >400 cells/mm^3 Certain HLA types are also associated with NVP-associated hepatic events but are population-specific.[a] Higher drug concentrations for PIs, particularly TPV	Prevention: Avoid concomitant use of hepatotoxic medications. If hepatic enzymes are elevated >5–10 times ULN, most clinicians would avoid NVP. Monitoring: *For ARVs other than NVP:* Obtain AST, ALT at baseline and thereafter at least every 3–4 months or more frequently in at-risk patients (such as HBV- or HCV-coinfected or elevated baseline AST, ALT). *For NVP:* Obtain AST, ALT at baseline, at 2 and 4 weeks, then every 3 months.	If a symptomatic hepatic event occurs on NVP, permanently discontinue drug (see also NVP hypersensitivity). In asymptomatic patients with ALT or AST >5–10 times ULN, some may consider discontinuing ARVs, others may continue therapy and monitor patient closely. In symptomatic patients, discontinue all ARVs and other potential hepatotoxic agents and avoid restart of the offending agent. When clinical hepatitis is associated with lactic acidosis, avoid restart of the most likely agent, and ZDV, d4T, and ddI in particular (see also lactic acidosis). Rule out coinfection with HAV, HBV, HCV, EBV, and CMV.

Table 17e. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Hepatic Events (Last updated November 1, 2012; last reviewed November 1, 2012) (page 2 of 2)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention / Monitoring	Management
Indirect hyperbilirubinemia	IDV, ATV	Onset: Early in therapy Presentation: Jaundice; Asymptomatic elevation of indirect bilirubin levels with normal direct bilirubin, AST, and ALT.	HIV-infected children receiving ATV: 49% developed increased total bilirubin levels (≥3.2 mg/dL); 13% had jaundice/scleral icterus.	Not associated with HBV or HCV	Monitoring: No specific monitoring.	Not necessary to discontinue the offending agent except for cosmetic reasons (hyperbilirubinemia may improve over time).
Non-cirrhotic portal hypertension	ARVs, especially ddI, d4T and combination of ddI and d4T	Onset: Late in therapy Presentation: GI bleeding, esophageal varices, hypersplenism. Mild elevations in AST and ALT, moderate increases in ALP, and pancytopenia (because of hypersplenism). Liver biopsy may reveal a variety of findings, most commonly nodular regenerative hyperplasia or hepatoportal sclerosis	Rare: Probably less than 1%	Prolonged exposure to ARV therapy, especially ddI and the combination of ddI and d4T	Monitoring: No specific monitoring.	Manage complications of GI bleeding and esophageal varices.

[a] HLA-DRB1*0101 in Caucasians, HLA-DRB1*0102 in South Africans, and HLA-B35 in Thai and Caucasians

Key to Acronyms: 3TC = lamivudine, ABC = abacavir, ALT = alanine transaminase, ALP = alkaline phosphatase, ARV = antiretroviral, AST = aspartate aminotransferase, ATV = atazanavir, CMV = cytomegalovirus, d4T = stavudine, ddI = didanosine, EBV = Epstein-Barr virus, FTC = emtricitabine, HAV = hepatitis A virus, HBV = hepatitis B virus, HCV = hepatitis C virus, IDV = indinavir, IRIS = immune reconstitution inflammatory syndrome, NNRTI = non-nucleoside reverse transcriptase inhibitor, NRTI = nucleoside reverse transcriptase inhibitor, NVP = nevirapine, PI = protease inhibitor, RAL = raltegravir, TDF = tenofovir, TPV = tipranavir, ULN = upper limit of normal, ZDV = zidovudine

Table 17f. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Insulin Resistance, Asymptomatic Hyperglycemia, Diabetes Mellitus (Last updated November 1, 2012; last reviewed November 1, 2012)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention / Monitoring	Management
Insulin resistance, asymptomatic hyperglycemia, DM[a]	Thymidine analogue NRTIs (d4T, ddI, ZDV) Some PIs (IDV, LPV/r; perhaps less often ATV, ATV/r, DRV/r, TPV/r)	Onset: Weeks to months after beginning therapy; median of 60 days (adult data) Presentation: *Most commonly:* Asymptomatic fasting hyperglycemia (possibly in the setting of lipodystrophy), metabolic syndrome, or growth delay *Also possible:* Frank DM (polyuria, polydipsia, polyphagia, fatigue, hyperglycemia)	Impaired fasting glucose: *ARV-treated adults:* 3%–25% *ARV-treated children:* 0%–7% Impaired glucose tolerance: *ARV-treated adults:* 16%–35% *ARV-treated children:* 3%–4% DM: *ARV-treated adults:* 0.6–4.7 per 100 person-years (2- to 4-fold greater than that for HIV-uninfected adults) *ARV-treated children:* Very rare in HIV-infected children	Risk factors for Type 2 DM: Lipodystrophy Metabolic syndrome Family history of DM High BMI Obesity	Prevention: Lifestyle modification (see Management). Although uncertain, avoiding use of d4T, IDV may reduce risk. Monitoring: Monitor for polydipsia, polyuria, polyphagia, change in body habitus, acanthosis nigricans. *Obtain RPG levels at*: Initiation of ARV therapy; 3–6 months after therapy initiation; and once a year thereafter. For RPG ≥140 mg/dL, obtain FPG performed after 8-hour fast and consider referral to endocrinologist.	Counsel on lifestyle modification (low-fat diet, exercise, no smoking). Consider changing from thymidine analogue NRTI (d4T or ZDV)-containing regimen. *For either RPG ≥200 mg/dL plus symptoms of DM or FPG ≥126 mg/dL:* Patient meets diagnostic criteria for DM; consult endocrinologist. *FPG 100–125 mg/dL:* Impaired FPG is suggestive of insulin resistance; consult endocrinologist. *FPG <100 mg/dL:* Normal FPG but does not exclude insulin resistance; recheck FPG in 6–12 months.

[a] Insulin resistance, asymptomatic hyperglycemia, and DM form a spectrum of increasing severity. *Insulin resistance* is often defined as elevated insulin levels for the level of glucose observed; *impaired FPG* as an FPG of 100–125 mg/dL; *impaired glucose tolerance* as an elevated 2-hour PG of 140–199 mg/dL in a standard OGTT; and *diabetes mellitus* as either an FPG ≥126 mg/dL, a random PG ≥200 mg/dL in a patient with hyperglycemia symptoms, an HgbA1C of ≥6.5%, or a 2-hour PG after OGTT ≥200 mg/dL. However, the Panel does not recommend routine determinations of insulin levels, HgbA1C, or glucose tolerance without consultation with an endocrinologist; these guidelines are instead based on the readily available random and fasting plasma glucose levels.

Key to Acronyms: ARV = antiretroviral, ATV = atazanavir, ATV/r = atazanavir/ritonavir, d4T = stavudine, ddI = didanosine, DM = diabetes mellitus, DRV/r = darunavir/ritonavir, FPG = fasting plasma glucose, IDV = indinavir, LPV/r = lopinavir/ritonavir, NRTI = nucleoside reverse transcriptase inhibitor, OGTT = oral glucose tolerance test, PG = plasma glucose, PI = protease inhibitor, RPG = random plasma glucose, TPV/r = tipranavir/ritonavir, ZDV = zidovudine

Table 17g. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Lactic Acidosis (Last updated November 1, 2012; last reviewed November 1, 2012)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention / Monitoring	Management
Lactic acidosis	NRTIs, in particular, d4T and ddI (alone and in combination)	Onset: 1–20 months after starting therapy (median onset 4 months in 1 case series). Presentation: Usually insidious onset of a combination of signs and symptoms: generalized fatigue, weakness, and myalgias; vague abdominal pain, weight loss, unexplained nausea or vomiting; dyspnea; peripheral neuropathy. Patients may present with acute multi-organ failure (such as fulminant hepatic, pancreatic, and respiratory failure).	Chronic, asymptomatic mild hyperlactatemia (2.1–5.0 mmol/L): *Adults:* 15%–35% of adults receiving NRTI therapy for longer than 6 months *Children:* 29%–32% Symptomatic severe hyperlactatemia (>5.0 mmol/L): *Adults:* 0.2%–5.7% Symptomatic lactic acidosis/hepatic steatosis: Rare in all age groups (*1.3–11 episodes per 1,000* person-years), but associated with a high fatality rate (33%–58%)	Adults: • Female gender • High BMI • Chronic HCV infection • African-American race • Prolonged NRTI use (particularly d4T and ddI) • Coadministration of ddI with other agents (such as d4T, TDF, RBV, or tetracycline) • Coadminstration of TDF with metformin • Overdose of propylene glycol • CD4 T lymphocyte count <350 cells/mm^3 • Acquired riboflavin or thiamine deficiency • Possibly, pregnancy Pre-term infants: • Use of propylene glycol (e.g., as an diluent for LPV/r)	Prevention: Avoid d4T and ddI in combination. Monitor for clinical manifestations of lactic acidosis and promptly adjust therapy. Monitoring: *Asymptomatic:* Measurement of serum lactate is not recommended. *Clinical signs or symptoms consistent with lactic acidosis:* Obtain blood lactate level;[a] additional diagnostic evaluations should include serum bicarbonate and anion gap and/or arterial blood gas, amylase and lipase, serum albumin, and hepatic transaminases.	Lactate 2.1–5.0 mmol/L (confirmed with second test): Consider replacing ddI and d4T with other ARVs. As alternative, temporarily discontinue all ARVs while conducting additional diagnostic workup. Lactate >5.0 mmol/L (confirmed with second test)[b] or >10.0 mmol/L (any one test): Discontinue all ARVs. Provide supportive therapy (intravenous fluids; some patients may require sedation and respiratory support to reduce oxygen demand and ensure adequate oxygenation of tissues). Anecdotal (unproven) supportive therapies: bicarbonate infusions, THAM, high-dose thiamine and riboflavin, oral antioxidants (e.g., L-carnitine, co-enzyme Q, vitamin C). Following resolution of clinical and laboratory abnormalities, resume therapy, either with an NRTI-sparing regimen or a revised NRTI-containing regimen instituted with caution, using NRTIs less likely to inhibit mitochondria (ABC or TDF preferred; possibly FTC or 3TC); and monthly monitoring of lactate for at least 3 months.

[a] Blood for lactate determination should be collected without prolonged tourniquet application or fist clenching into a pre-chilled, gray-top, fluoride-oxalate-containing tube and transported on ice to the laboratory to be processed within 4 hours of collection.

[b] Management can be initiated before the results of the confirmatory test.

Key to Abbreviations: 3TC = lamivudine, ABC = abacavir, ARVs = antiretrovirals, BMI = body mass index, d4T = stavudine, ddI = didanosine, FTC = emtricitabine, HCV = hepatitis C virus, LPV/r = lopinavir/ritonavir, NRTI = nucleoside reverse transcriptase inhibitor, RBV = ribavirin, TDF = tenofovir disoproxil fumarate, THAM = tris–hydroxymethyl-aminomethane

Table 17h. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Lipodystrophy, Lipohypertrophy, Lipoatrophy (Last updated November 1, 2012; last reviewed November 1, 2012)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention / Monitoring	Management
Lipodystrophy (fat redistribution)—general information	See below for specific associations.	Onset: Trunk and limb fat initially increases within a few months of start of ART; peripheral fat wasting may not begin to appear for 12 to 24 months.	Adults: 2%–84% Children: 1%–33%, perhaps more common in adolescents than prepubertal children	Genetic predisposition Puberty HIV-associated inflammation Older age Longer duration of ART	See below	See below
Central lipohypertrophy	Can occur in the absence of ART, but most associated with PIs and EFV; EFV also associated with gynecomastia and breast hypertrophy	Presentation: Central fat accumulation with increased abdominal girth, which may include dorsocervical fat pad (buffalo hump) and/or gynecomastia in males or breast hypertrophy in females. The appearance of central lipohypertrophy is accentuated in the presence of peripheral fat wasting (lipoatrophy).	Up to 25%	Obesity before initiation of therapy Sedentary lifestyle	Prevention: Calorically appropriate, low-fat diet and exercise. Monitoring: Measure BMI.	Calorically appropriate, low-fat diet and exercise, especially strength training. Smoking cessation (if applicable) to decrease future CVD risk. Data are insufficient to allow the Panel to safely recommend use of any of the following modalities in children: recombinant human growth hormone, growth hormone-releasing hormone, metformin, thiazolidinediones, anabolic steroids, or liposuction.
Facial/peripheral lipoatrophy	Most associated with thymidine analogue NRTI (d4T > ZDV)	Presentation: Thinning of subcutaneous fat in face, buttocks, and extremities, measured as decrease in trunk/limb fat by DXA or triceps skinfold thickness. Preservation of lean body mass distinguishes lipoatrophy from HIV-associated wasting.	Risk low (up to 15%) in patients not treated with d4T or ZDV	d4T and ZDV Obesity before ART	Prevention: Avoid use of d4T and ZDV. Monitoring: Patient self-report and physical exam are the most sensitive methods of monitoring lipoatrophy.	Switch from d4T or ZDV to other NRTIs if possible without loss of virologic control. Data are insufficient to allow the Panel to safely recommend use of any of the following modalities in children: injections of poly-L-lactic acid, recombinant human leptin, autologous fat transplantation, or thiazolidinediones.

Key to Acronyms: ARV = antiretroviral, BMI = body mass index, ART = antiretroviral therapy. CVD = cardiovascular disease, d4T = stavudine, DXA = dual energy x-ray absorptiometry, EFV = efavirenz, NRTI = nucleoside reverse transcriptase inhibitor, PI = protease inhibitor, ZDV = zidovudine

Table 17i. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Nephrotoxic Effects (Last updated November 1, 2012; last reviewed November 1, 2012)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention / Monitoring	Management
Urolithiasis/ nephrolithiasis	IDV, ATV	Onset: Weeks to months after starting therapy Clinical findings: Crystalluria, hematuria, pyuria, flank pain, sometimes increased creatinine	IDV-related nephrolithiasis is more common in adults (4%–43%) than in children (0%–20%). ATV nephrolithiasis rare	In adults, high serum IDV concentrations and elevated urine pH (>5.7) associated with persistent pyuria. Unknown in children.	Prevention: Maintain adequate hydration. Monitoring: Obtain urinalysis at least every 6–12 months.	Provide adequate hydration and pain control; consider using alternative ARV agent.
Renal dysfunction	TDF	Onset: Variable; in adults, weeks to months after initiation of therapy. Hypophosphatemia appears at a median of 18 months. Presentation: Renal failure, acute tubular necrosis, Fanconi syndrome, proximal renal tubulopathy, interstitial nephritis (including acute cases), nephrogenic diabetes insipidus, renal insufficiency, increased creatinine, proteinuria, polyuria	Adults: ~2% with increased serum creatinine; ~0.5% with severe renal complications Children: ~4% with hypophosphatemia or proximal tubulopathy; 25% to 78% with severe proteinuria (may be confounded by advanced HIV infection in children studied, and concomitant use of ddI)	Risk may be increased in children aged >6 years, black race, Hispanic/Latino ethnicity, and by advanced HIV infection, concurrent use of ddI or PIs (especially LPV/r), and pre-existing renal dysfunction).	Urinalysis, measurement of serum creatinine, calcium, and phosphorus and determination of spot urine protein/creatinine ratios at least every 6–12 months.	If TDF is the likely cause, consider using alternative medication.
	IDV	Renal cortical atrophy, acute renal failure	Rare	Unknown	Unknown	If IDV is likely cause, consider using alternative medication.

Key to Acronyms: ARV = antiretroviral, ATV = atazanavir, ddI = didanosine, IDV = indinavir, LPV/r = lopinavir/ritonavir, PI = protease inhibitor, TDF = tenofovir disoproxil fumarate

Table 17i. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Nephrotoxic Effects (Last updated November 1, 2012; last reviewed November 1, 2012)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention / Monitoring	Management
Urolithiasis/ nephrolithiasis	IDV, ATV	Onset: Weeks to months after starting therapy Clinical findings: Crystalluria, hematuria, pyuria, flank pain, sometimes increased creatinine	IDV-related nephrolithiasis is more common in adults (4%–43%) than in children (0%–20%). ATV nephrolithiasis rare	In adults, high serum IDV concentrations and elevated urine pH (>5.7) associated with persistent pyuria. Unknown in children.	Prevention: Maintain adequate hydration. Monitoring: Obtain urinalysis at least every 6–12 months.	Provide adequate hydration and pain control; consider using alternative ARV agent.
Renal dysfunction	TDF	Onset: Variable; in adults, weeks to months after initiation of therapy. Hypophosphatemia appears at a median of 18 months. Presentation: Renal failure, acute tubular necrosis, Fanconi syndrome, proximal renal tubulopathy, interstitial nephritis (including acute cases), nephrogenic diabetes insipidus, renal insufficiency, increased creatinine, proteinuria, polyuria	Adults: ~2% with increased serum creatinine; ~0.5% with severe renal complications Children: ~4% with hypophosphatemia or proximal tubulopathy; 25% to 78% with severe proteinuria (may be confounded by advanced HIV infection in children studied, and concomitant use of ddI)	Risk may be increased in children aged >6 years, black race, Hispanic/Latino ethnicity, and by advanced HIV infection, concurrent use of ddI or PIs (especially LPV/r), and pre-existing renal dysfunction).	Urinalysis, measurement of serum creatinine, calcium, and phosphorus and determination of spot urine protein/creatinine ratios at least every 6–12 months.	If TDF is the likely cause, consider using alternative medication.
	IDV	Renal cortical atrophy, acute renal failure	Rare	Unknown	Unknown	If IDV is likely cause, consider using alternative medication.

Key to Acronyms: ARV = antiretroviral, ATV = atazanavir, ddI = didanosine, IDV = indinavir, LPV/r = lopinavir/ritonavir, PI = protease inhibitor, TDF = tenofovir disoproxil fumarate

Table 17j. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Osteopenia, Osteoporosis, Osteonecrosis (page 2 of 2) (Last updated November 1, 2012; last reviewed November 1, 2012)

[a] Some experts would periodically measure 25-OH-vitamin D, especially in HIV-infected urban youth because, in this population, the prevalence of vitamin D insufficiency is high.

[b] Until more data are available about the long-term effects of tenofovir on bone mineral acquisition in childhood, some experts would obtain a DXA at baseline and every 6 to 12 months for prepubertal children and children in early puberty who are initiating treatment with tenofovir. DXA should also be obtained in children with indications not uniquely related to HIV infection (such as cerebral palsy).

Key to Acronyms: ARVs = antiretrovirals, BMD = bone mineral density, BMI = body mass index, cART = combination antiretroviral therapy, CT = computed tomography, d4T = stavudine, DXA = dual energy x-ray absorptiometry, MRI = magnetic resonance imaging, PIs = protease inhibitors, TDF = tenofovir disoproxil fumarate

Table 17k. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Peripheral Nervous System Toxicity (Last updated November 1, 2012; last reviewed November 1, 2012)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency [a]	Risk Factors	Prevention/Monitoring	Management
ARV toxic neuropathy[b]	d4T, ddI	Onset: Variable, weeks to months following NRTI initiation Presentation: Decreased sensation Aching, burning, painful numbness Hyperalgesia (lowered pain threshold) Allodynia (non-noxious stimuli cause pain) Decreased or absent ankle reflexes Distribution: bilateral soles of feet, ascending to legs and fingertips	HIV-infected children: 1.13% prevalence (baseline 2001); 0.23 per 100 person-years (2001–2006) 0.07%–0.26% incidence in two large African cohorts (aged 1 month–18 years, median follow-up 1.8–3.2 years) HIV-infected adults: 17%–57% taking d4T	HIV-infected adults: Pre-existing neuropathy (diabetes, alcohol abuse, vitamin B_{12} deficiency) Elevated triglyceride levels Older age Poor nutrition More advanced HIV disease Mitochondrial DNA haplogroup	Limit use of d4T and ddI, if possible. As part of routine care, monitor for symptoms and signs of peripheral neuropathy.	Discontinue offending agent. Persistent pain can be difficult to treat; topical capsaicin 8% may be helpful. Data are insufficient to allow the Panel to safely recommend use of any of the following modalities in children: tricyclic antidepressants, gabapentin, pregabalin, mexilitine, or lamotrigine.

[a] Peripheral neuropathy may be underreported in children because symptoms are difficult to evaluate in young children.

[b] HIV infection itself may cause a distal sensory neuropathy that is phenotypically identical to ARV toxic neuropathy.

Key to Acronyms: ARV = antiretroviral, d4T = stavudine, ddI = didanosine, NRTI = nucleoside reverse transcriptase inhibitor

Table 17I. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Rash, SJS/EM/TEN, HSR (page 1 of 4) (Last updated November 1, 2012; last reviewed November 1, 2012)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/Monitoring	Management
Rash	Any ARV can cause rash.	Onset: First few days to weeks after starting therapy Presentation: Most rashes are mild-to-moderate, diffuse maculopapular eruptions. Some rashes are a manifestation of systemic hypersensitivity (see also HSR).	Common (>10% adults and/or children): NVP, EFV, ETR, FPV, ATV, FTC Less common (5%–10%): ABC, DRV, TPV, TDF Unusual (2%–4%): LPV/r, RAL, MVC, RPV	• Sulfonamide allergy is a risk factor for rash with PIs containing a sulfonamide moiety (FPV, DRV, TPV). • Possible association of polymorphisms in CYP2B6 and multiple HLA loci with rash with NVP.	• When starting NVP or restarting after interruptions >14 days: Once-daily dosing (50% of total daily dose) for 2 weeks, then escalation to target dose with twice-daily dosing is associated with fewer rashes.[a] Avoid use of corticosteroids during NVP dose escalation. • Assess patient for concomitant medications and illnesses that cause rash, rash severity, mucosal involvement, and presence of systemic signs and symptoms (see also HSR).	*Mild-to-moderate maculopapular rash without systemic or mucosal involvement:* Prescribe antihistamine as needed; ARV medication can be continued.[a] *Severe rash (accompanied by blisters, fever, involvement of the mucous membranes, conjunctivitis, edema, arthralgias):* • Discontinue all ARVs and other possible causative agents such as cotrimoxazole. Do not restart the offending medication. (See SJS/EM/TEN.) • In case of SJS/EM/TEN with one NNRTI, many experts would avoid use of other NNRTIs. If rash develops with NVP treatment, measure hepatic transaminases. If hepatic transaminases are elevated, NVP should be discontinued and not restarted (see NVP hypersensitivity).
	ENF	Onset: First few days to weeks after starting therapy Presentation: Local injection site reactions with pain, erythema, induration, nodules and cysts, pruritis, ecchymosis. Often multiple reactions at the same time.	Adults and children: >90%	Unknown	• During routine visits, assess patient for local reactions. • Rotate injection sites. • Massage area after injection.	• Continue the agent as tolerated by the patient. • Adjust injection technique. • Rotate injection sites.

Table 17l. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Rash, SJS/EM/TEN, HSR (page 2 of 4) (Last updated November 1, 2012; last reviewed November 1, 2012)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/Monitoring	Management
SJS/EM major/TEN	Many ARVs, especially NNRTIs (see frequency column)	Onset: First few days to weeks after initiating therapy Presentation: Skin eruption occurs with mucous membrane ulceration, conjunctivitis. Can evolve into blister/bulla formation and can progress to skin necrosis. Systemic symptoms may include fever, tachycardia, malaise, myalgia, and arthralgia.	Infrequent: NVP (0.3%), EFV (0.1%), ETR (<0.1%) Case reports: FPV, ABC, DRV, ZDV, ddI, IDV, LPV/r, ATV, RAL	Adults: • Female gender • Race/ethnicity (black, Asian, Hispanic)	• *When starting NVP or restarting after interruptions >14 days:* Once-daily dosing (50% of total daily dose) for 2 weeks, then escalation to target dose with twice-daily dosing is associated with fewer rashes.[a] • Counsel families to report symptoms as soon as they appear.	• Discontinue all ARVs and other possible causative agents such as cotrimoxazole. • Provide intensive supportive care, IV hydration, aggressive wound care, pain management, antipyretics, parenteral nutrition, and antibiotics as needed in case of superinfection. • Corticosteroids and/or IVIG are sometimes used but use of each is controversial. • Do not reintroduce the offending medication. • In case of SJS/EM/TEN with one NNRTI, many experts would avoid use of other NNRTIs.
Systemic HSR (with or without skin involvement and excluding SJS)	ABC	Onset: *With first use:* within first 6 weeks *With reintroduction:* within hours Presentation: Symptoms include high fever, diffuse skin rash, malaise, nausea, headache, myalgia, arthralgia, diarrhea, vomiting, abdominal pain, pharyngitis, respiratory symptoms such as dyspnea. Symptoms worsen to include hypertension and vascular collapse with continuation. With rechallenge, symptoms can mimic anaphylaxis.	2.3%–9% (varies by racial/ethnic group)	• HLA-B*5701 (HSR very uncommon in people who are HLA-B*5701 negative); also HLA-DR7, HLA-DQ3. • Whites are at much greater risk of HSR than blacks or Asians.	• Screen for HLA- B*5701. ABC should not be prescribed if HLA-B*5701 is positive. The medical record should clearly indicate that the patient is ABC allergic. • Counsel patients and families about the signs and symptoms of HSR to ensure prompt reporting of reactions.	• Discontinue ARVs and investigate for other causes of the symptoms, such as an intercurrent viral illness. • Treat symptoms as necessary. • Most symptoms resolve within 48 hours after discontinuation of ABC. • Do not rechallenge with ABC even if the patient is HLA-B*5701 negative.

Table 17l. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Rash, SJS/EM/TEN, HSR (page 3 of 4) (Last updated November 1, 2012; last reviewed November 1, 2012)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/Monitoring	Management
Systemic HSR (with or without skin involvement and excluding SJS)	NVP	Onset: Most frequent in the first few weeks of therapy but can occur through 18 weeks. Presentation: Flu-like symptoms (including nausea, vomiting, myalgia, fatigue, fever, abdominal pain, jaundice) with or without skin rash that may progress to hepatic failure with encephalopathy. DRESS syndrome has also been described.	4% (2.5%–11%)	Adults: • Treatment-naive with higher CD4 count (>250 cells/mm^3 in women; >400 cells/mm^3 in men). • Female gender (Risk is 3-fold higher in females compared with males.) Children: NVP hepatoxicitiy and hypersensitivity are less common in prepubertal children than in adults. The PREDICT Study showed a 2.65 times higher risk of overall NVP toxicity (rash, hepatotoxicity, hypersensitivity) in children with CD4 ≥15% compared to children with CD4 <15%.	• 2-week lead-in period for start or restart for interruptions >14 days with once-daily dosing then dose escalation to twice daily as recommended may reduce rash and hepatic events.[a] • Counsel families about signs and symptoms of HSR to ensure prompt reporting of reactions. • Obtain AST and ALT in patients with rash. Obtain AST and ALT at baseline, before dose escalation, 2 weeks post dose escalation, and thereafter at 3-month intervals. • Avoid NVP use in women with CD4 counts >250 cells/mm^3 and in men with CD4 counts >400 cells/mm^3 unless benefits outweigh risks. • Do not use NVP in postexposure prophylaxis.	• Discontinue ARVs. • Consider other causes for hepatitis and discontinue all hepatotoxic medications. • Provide supportive care as indicated and monitor patient closely. • Do not reintroduce NVP. The safety of other NNRTIs is unknown following symptomatic hepatitis due to NVP, and many experts would avoid the NNRTI drug class when restarting treatment.

Table 17l. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Rash, SJS/EM/TEN, HSR (page 4 of 4) (Last updated November 1, 2012; last reviewed November 1, 2012)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/Monitoring	Management
Systemic HSR (with or without skin involvement and excluding SJS)	ENF, ETR	Onset: Any time during therapy. Presentation: Symptoms may include rash, constitutional findings, and sometimes organ dysfunction including hepatic failure.	Rare	Unknown	Evaluate for hypersensitivity if the patient is symptomatic.	Discontinue ARVs. Rechallenge is not recommended.
	RAL	DRESS syndrome	Case report	Unknown	Evaluate for hypersensitivity if the patient is symptomatic.	Discontinue all ARVs. Rechallenge with RAL is not recommended.
	MVC	Rash preceding hepatotoxicity	Rare	Unknown	Obtain AST and ALT in patients with rash or other symptoms of hypersensitivity.	Discontinue all ARVs. Rechallenge with MVC is not recommended.

[a] The prescribing information for NVP states that patients experiencing rash during the 14-day lead-in period should not have the NVP dose increased until the rash has resolved. However, prolonging the lead-in phase beyond 14 days may increase risk of NVP resistance because of subtherapeutic drug levels. Management of children who have persistent mild or moderate rash after the lead-in period should be individualized and consultation with an expert in HIV care should be obtained. NVP should be stopped if the rash is severe or is worsening or progressing.

Key to Acronyms: ABC = abacavir, ALT = alanine transaminase, ARVs = antiretrovirals, AST = aspartate aminotransferase, ATV = atazanavir, ddI = didanosine, DRESS = drug rash with eosinophilia and systemic symptoms, DRV = darunavir, EFV = efavirenz, EM = erythema multiforme, ENF = enfuvirtide, ETR = etravirine, FPV = fosamprenavir, FTC = emtricitabine, HSR = hypersensitivity reaction, IDV = indinavir, IV = intravenous, IVIG = intravenous immune globulin, LPV/r = lopinavir/ritonavir, MVC = maraviroc, NNRTI = non-nucleoside reverse transcriptase inhibitor, NVP = nevirapine, PI = protease inhibitor, RAL = raltegravir, RPV = rilpivirine, SJS = Stevens Johnson syndrome, TDF = tenofovir disoproxil fumarate, TEN = toxic epidermal necrolysis, TPV = tipranavir, ZDV = zidovudine

Table 18. Definitions of Treatment Failure in HIV-Infected Children

Virologic Failure[a]	• **Incomplete virologic response to therapy:** Incomplete virologic response to therapy is defined as:
	  • <1.0 $\log_{10}$ decrease in HIV RNA copy number from baseline after 8–12 weeks of therapy, or
	  • HIV RNA >200 copies/mL after 6 months of therapy, or
	  • repeated HIV RNA above the level of quantification using the most sensitive assay after 12 months of therapy.[a]
	• **Viral rebound:** Viral rebound is defined as repeated detection of plasma HIV RNA above the level of quantification after a child had achieved virologic suppression in response to therapy. Isolated episodes of plasma HIV RNA detection above the level of quantification but <1,000 copies/mL are common. They generally do not indicate virologic failure and may be transient blips, but should be followed up to confirm spontaneous resolution.

Immunologic Failure[b]	• **Incomplete immunologic response to therapy:** Failure in a child aged <5 years with severe immune suppression (CD4 percentage <15%) of CD4 percentage to increase by ≥5 percentage points or failure in a child aged ≥5 years with severe immune suppression (CD4 < 200 cells/mm^3) of absolute CD4 cell counts to increase 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 pre-therapy baseline at any age or decline to below pre-therapy baseline in absolute CD4 cell count in children aged ≥5 years.[c]
Clinical Failure	• **Progressive neurodevelopmental deterioration:** Two or more of the following on repeated assessments: impairment in brain growth, decline in cognitive function documented by psychometric testing, and 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.

[a] Children with higher plasma HIV RNA levels at initiation of therapy, especially infants, may take longer to reach undetectable viral load.[7] HIV-infected adults with HIV RNA detectable above the level of quantification but <200 copies/mL after 6 months of cART often ultimately achieve virologic suppression without regimen change.[9]

[b] At least 2 measurements (taken at least 1 week apart) should be performed to confirm initial laboratory results.

[c] Declines that represent a change to a more advanced category of immunosuppression compared with baseline (such as from CD4 percentage of 28% to 23% or from CD4 cell count of 250 cells/mm^3 to 150 cells/mm^3) or to more severe immunosuppression in those already suppressed at baseline (such as from CD4 percentage of 14% to 9% or from CD4 cell count of 150 cells/mm^3 to 100 cells/mm^3) are of particular concern.

Table 19. Assessment of Causes of Virologic Antiretroviral Treatment Failure (page 1 of 2)

Cause of Virologic Treatment Failure	Assessment Method	Intervention
Non-Adherence	1. Interview child and caretaker • Take 24-hour or 7-day recall • Obtain description of: • *WHO* gives medications • *WHEN* medications are taken/given • *WHAT* medications are taken/given (names, doses) • *WHERE* medications are kept/ administered • Have open-ended discussion of experiences taking/giving medications and barriers/challenges 2. Review pharmacy records • Assess timeliness of refills	• Identify or re-engage family members to support/supervise adherence • Establish fixed daily times and routines for medication administration • To avoid any patient/caregiver confusion with drug names, explain that drug therapies have generic names and trade names, and many agents are co-formulated under a third or fourth name. • Explore opportunities for facility or home-based DOT
	3. Observe medication administration • Observe dosing/administration in clinic • Conduct home-based observation by visiting health professional • Admit to hospital for trial of therapy • Observe administration/tolerance • Monitor treatment response	• Simplify medication regimen, if feasible • Substitute new agents if single ARV is poorly tolerated • Consider gastric tube placement to facilitate adherence • Consider DOT • Use tools to simplify administration (e.g., pill boxes, reminders [including alarms], integrated medication packaging for AM or PM dosing) • Suggest relaxation techniques
	4. Conduct psychosocial assessment • Make a comprehensive family-focused assessment of factors likely to impact adherence with particular attention to recent changes: • Status of caregiver, housing, financial stability of household, child/caretaker relationships, school, and child's achievement level • Substance abuse (child, caretaker, family members) • Mental health and behavior • Child/youth and caretaker beliefs about cART • Disclosure status (to child and others)	• 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 protective services and alternate care settings when necessary

Table 19. Assessment of Causes of Virologic Antiretroviral Treatment Failure (page 2 of 2)

Cause of Virologic Treatment Failure	Assessment Method	Intervention
Pharmaco-kinetics and Dosing Issues	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 ARV drugs (see Role of Therapeutic Drug Monitoring in Management of Treatment Failure).	• Adjust drug doses • Discontinue or substitute competing medications • Reinforce applicable food restrictions
ARV Drug Resistance	1. Perform resistance testing, as appropriate (see Antiretroviral Drug- Resistance Testing).	• If minimal or no resistance detected to current drugs, focus on improving adherence • If resistance to current regimen detected, optimize adherence and evaluate potential for new regimen (see Approach to the Management of Virologic Failure of Antiretroviral Treatment).

Key to Acronyms: ARV = antiretroviral, cART = combination antiretroviral therapy, DOT = directly observed therapy

Table 20. Options for Regimens with at Least Two Fully Active Agents with Goal of Virologic Suppression in Patients With Failed Antiretroviral Therapy and Evidence of Viral Resistance[a]

Prior Regimen	Recommended Change (in order of relative preference)[a]
2 NRTIs + NNRTI	• 2 NRTIs + PI • 2 NRTI + integrase inhibitor[b]
2 NRTIs + PI	• 2 NRTIs + NNRTI • 2 NRTIs + alternative RTV-boosted PI • 2 NRTIs + integrase inhibitor[b] • NRTI(s) + integrase inhibitor + (NNRTI *or* alternative RTV-boosted PI)
3 NRTIs	• 2 NRTIs + (NNRTI or PI) • 2 NRTIs + integrase inhibitor[b] • Integrase inhibitor[b] + 2 other active agents (chosen from NNRTI, PI, NRTI[s])
Failed regimen(s) that included NRTI(s), NNRTI(s), and PI(s)	• > 1 NRTI + RTV-boosted PI • NRTI(s) + RTV-boosted PI + integrase inhibitor[b] (consider adding T-20 and/or MVC,[c] if additional active drug[s] needed) • NRTI(s) + RTV-boosted DRV, LPV or SQV + ETR (consider adding one or more of MVC,[c] T-20, or integrase inhibitor,[b] if additional active drug[s] needed) • > 1 NRTI + 2 RTV-boosted PIs (LPV/r + SQV, LPV/r + ATV) (consider adding T-20 or an integrase inhibitor[b] if additional active drug[s] needed)

[a] ARV regimens should be chosen based on treatment history and drug-resistance testing to optimize ARV drug effectiveness. This is particularly important in selecting NRTI components of an NNRTI-based regimen where drug resistance to the NNRTI can occur rapidly 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. *Please see individual drug profiles for information about drug interactions and dose adjustment when devising a regimen for children with multi-class drug resistance.* Collaboration with a pediatric HIV specialist is especially important when choosing regimens for children with multi-class drug resistance. Regimens in this table are listed in relative order of preference and are provided as examples but the list is not exhaustive.

[b] Caution advised when using raltegravir in children aged ≤6 years because pharmacokinetic and efficacy data are particularly limited in this age group.

[c] No current FDA-approved pediatric indication for maraviroc.

Key to Acronyms: ATV = atazanavir, DRV = darunavir, ETR = etravirine, LPV = lopinavir, LPV/r = lopinavir/ritonavir, MVC = maraviroc, NNRTI = non-nucleoside reverse transcriptase inhibitor, NRTI = nucleoside reverse transcriptase inhibitor, PI = protease inhibitor, RTV = ritonavir, SQV = saquinavir, T-20 = enfuvirtide

Table 21. Suggested Minimum Target Trough Concentrations[a]

Drug	Concentration (ng/mL)
Atazanavir	150
Fosamprenavir	400 (measured as amprenavir concentration)
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

[a] Reprinted from: *Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents*. Department of Health and Human Services. http://aidsinfo.nih.gov/contentfiles/lvguidelines/adultandadolescentgl.pdf.