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 ARV agents in infants, children, and adolescents (through mid-puberty) living with HIV in the United States.
Panel Members	The Panel is composed of approximately 35 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 (e.g., parents and caregivers of children and youth living with HIV). The Panel also includes at least one representative from each of the following 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 an annual financial disclosure statement in writing, 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 infants, children, and adolescents living with HIV in the United States
Developer	Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV—a working group of OARAC
Funding Source	Office of AIDS Research, NIH and HRSA
Evidence Collection	A standardized review of recent, relevant literature related to each section of the guidelines is performed by a technical assistance consultant (through funding from HRSA) and provided to individual Panel section working groups. The recommendations are generally based on studies published in peer-reviewed journals. The Panel may occasionally use unpublished data to revise the guidelines, particularly when the new information relates to dosing or patient safety. These data come from presentations at major conferences or from the FDA and/or drug manufacturers.
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 all proposals during monthly teleconferences. Proposals are modified based on Panel discussion and then distributed with ballots to all Panel members for concurrence and additional comments. If there are substantive comments or votes against approval, the recommended changes and areas of disagreement are brought back to the full Panel (by email or teleconference) for additional review, discussion, and further modification to reach a final version acceptable to all Panel members. The recommendations in these final versions represent endorsement from a consensus of members and are included in the guidelines as official Panel recommendations.
Other Guidelines	These guidelines focus on infants, children, and adolescents in early puberty (SMR I–III) living with HIV. Guidance for treatment of adolescents in late puberty (SMR IV–V) is provided by the Panel on Antiretroviral Guidelines for Adults and Adolescents. Separate guidelines outline the use of ART in pregnant women with HIV infection (including maternal and infant interventions for prevention of perinatal transmission), ART for nonpregnant adults and postpubertal adolescents with HIV infection, and ARV prophylaxis for those who experience occupational or nonoccupational exposure to HIV. These guidelines are also available on the AIDS*info* website (http://www.aidsinfo.nih.gov).
Update Plan	The full Panel meets monthly by teleconference to review data that may warrant modification of the guidelines. Smaller working groups of Panel members hold additional teleconferences to review individual drug sections or other specific topics (e.g., What to Start). 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. All sections of the guidelines will be reviewed, with updates as appropriate, at least once a year.
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[a] 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[a] 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[a] with long-term clinical outcomes **II*:** One or more well-designed, nonrandomized trials or observational cohort studies in adults with long-term clinical outcomes plus accompanying data in children[a] from one or more smaller nonrandomized trials or cohort studies with clinical outcome data **III:** Expert opinion

[a] Studies that include children or children and adolescents, but not studies limited to post-pubertal adolescents

Table 3. Sample Schedule for Clinical and Laboratory Monitoring of Children Before and After Initiation of Antiretroviral Therapy

	Entry Into Care[a]	Pre-Therapy[b]	ART Initiation[c]	Weeks 1–2 on Therapy	Weeks 2–4 on Therapy	Every 3–4 Months[d]	Only Required Every 6–12 Months[e]	ARV Switch
History and Physical	√	√	√	√	√	√		√
Adherence Evaluation		√	√	√	√	√		√
CD4 Count	√	√	√			√		√
Plasma Viral Load	√	√	√		√	√		√
Resistance Testing	√							√
CBC with Differential	√	√	√		√	√		√
Chemistries[f]	√	√	√		√	√		√
Lipid Panel	√		√				√	
Random Plasma Glucose[g]			√				√	
Urinalysis	√		√				√	
Hepatitis B Screening[h,i]		√						√

[a] See text for details on recommended laboratory tests to obtain.

[b] Readiness for ARV adherence is assessed prior to starting ART. If abacavir is being considered as part of the regimen, send HLA-B*5701 testing prior to initiation of that ARV and choose an alternative ARV if HLA-B*5701 is positive (see Abacavir in Appendix A: Pediatric Antiretroviral Drug Information). Genotype resistance testing is recommended if not already performed (see Antiretroviral Drug-Resistance Testing in the Adult and Adolescent Antiretroviral Guidelines). Send tests appropriate to the toxicities expected from each patient's ART regimen and history (see text).

[c] If ART is initiated within 30 to 90 days of a pre-therapy lab result, repeat testing may not be necessary.

[d] CD4 cell count, CBC, and chemistries can be monitored less frequently (every 6–12 months) in children and youth who are adherent to therapy and have CD4 cell values well above the threshold for opportunistic infection risk, sustained viral suppression, and stable clinical status for more than 2 to 3 years. Viral load testing every 3 to 4 months is generally recommended to monitor ARV adherence.

[e] If lipids have been abnormal in the past, more frequent monitoring might be needed. For patients treated with TDF, more frequent urinalysis should be considered.

[f] Chemistries refer to a comprehensive metabolic panel.

[g] Random plasma glucose collected in a gray top tube.

[h] Recommended when considering starting ARV drugs with activity against hepatitis B, specifically lamivudine-, emtricitabine-, and tenofovir-containing regimens.

[i] Recommended only when individual previously demonstrated no immunity to hepatitis B.

Key to Acronyms: ART = antiretroviral therapy; ARV = antiretroviral; CBC = complete blood count; CD4 = CD4 T lymphocyte; TDF = tenofovir disoproxil fumarate

Table 4. Primary, FDA-Approved Assays to Monitor Viral Load

Assay	Abbott Real Time	NucliSens EasyQ v 2.0	COBAS Ampliprep/ TaqMan v 2.0	Versant v 1.0
Method	Real-time RT-PCR	Real-time NASBA	Real-time RT-PCR	Real-time RT-PCR
Dynamic Range (copies/mL)	40–10^7	25–10^7	20–10^7	37–11x10^7
Specimen volume[a]	0.2–1 mL	0.1–1 mL	1 mL	0.5 mL
Manufacturer	Abbott	bioMerieux	Roche	Siemens

[a] Smaller volumes for children can be accommodated.

Key to Acronyms: FDA = Food and Drug Administration; NASBA = nucleic acid sequence-based amplification; RT-PCR = reverse transcription polymerase chain reaction

Table 5. HIV Infection Stage[a] Based on Age-Specific CD4 Cell Count or Percentage

Stage	Age on Date of CD4 Test					
	<1 Year	%	1 to <6 Years	%	≥6 Years	%
	Cells/µL		Cells/µL		Cells/µL	
1	≥1,500	≥34	≥1,000	≥30	≥500	≥26
2	750–1,499	26–33	500–999	22–29	200–499	14–25
3	<750	<26	<500	<22	<200	<14

[a] The stage is based primarily on the CD4 cell count; the CD4 cell count takes precedence over the CD4 percentage, and the percentage is considered only if the count is missing. If a Stage 3-defining opportunistic illness has been diagnosed (Table 6), then the stage is 3 regardless of CD4 test results.

Source: Centers for Disease Control and Prevention. Revised surveillance case definition for HIV infection—United States, 2014. *MMWR* 2014;63(No. RR-3):1-10.

Key to Acronyms: CD4 = CD4 T lymphocyte

Table 6. HIV-Related Symptoms (page 1 of 2)

Mild HIV-Related Symptoms
Children with 2 or more of the conditions listed, but none of the conditions listed in Moderate Symptoms category: • Lymphadenopathy (≥0.5 cm at more than 2 sites; bilateral at 1 site) • Hepatomegaly • Splenomegaly • Dermatitis • Parotitis • Recurrent or persistent upper respiratory tract infection, sinusitis, or otitis media
Moderate HIV-Related Symptoms
• Anemia (hemoglobin <8 g/dL [<80 g/L]), neutropenia (white blood cell count <1,000/μL [<1.0 × 10^9/L]), and/or thrombocytopenia (platelet count <100 × 10^3/μL [<100 × 10^9/L]) persisting for ≥30 days • Bacterial meningitis, pneumonia, or sepsis (single episode) • Candidiasis, oropharyngeal (thrush), persisting (>2 months) in children aged >6 months • Cardiomyopathy • Cytomegalovirus infection, with onset before 1 month • Diarrhea, recurrent or chronic • Hepatitis • Herpes simplex virus (HSV) stomatitis, recurrent (>2 episodes within 1 year) • HSV bronchitis, pneumonitis, or esophagitis with onset before 1 month • Herpes zoster (shingles) involving at least 2 distinct episodes or more than 1 dermatome • Leiomyosarcoma • Lymphoid interstitial pneumonia or pulmonary lymphoid hyperplasia complex • Nephropathy • Nocardiosis • Persistent fever (lasting >1 month) • Toxoplasmosis, onset before 1 month • Varicella, disseminated (complicated chickenpox)

Table 6. HIV-Related Symptoms (page 2 of 2)

Stage-3-Defining Opportunistic Illnesses in HIV Infection
• Bacterial infections, multiple or recurrent[a]
• Candidiasis of bronchi, trachea, or lungs
• Candidiasis of esophagus
• Cervical cancer, invasive[b]
• Coccidioidomycosis, disseminated or extrapulmonary
• Cryptococcosis, extrapulmonary
• Cryptosporidiosis, chronic intestinal (>1 month duration)
• Cytomegalovirus disease (other than liver, spleen, or nodes), onset at age >1 month
• Cytomegalovirus retinitis (with loss of vision)
• Encephalopathy attributed to HIV[c]
• HSV: chronic ulcers (>1 month duration) or bronchitis, pneumonitis, or esophagitis (onset at age >1 month)
• Histoplasmosis, disseminated or extrapulmonary
• Isosporiasis, chronic intestinal (>1 month duration)
• Kaposi sarcoma
• Lymphoma, Burkitt (or equivalent term)
• Lymphoma, immunoblastic (or equivalent term)
• Lymphoma, primary, of brain
• *Mycobacterium avium* complex or *Mycobacterium kansasii*, disseminated or extrapulmonary
• *Mycobacterium tuberculosis* of any site, pulmonary, disseminated, or extrapulmonary
• *Mycobacterium*, other species or unidentified species, disseminated or extrapulmonary
• *Pneumocystis jirovecii* (previously known as *Pneumocystis carinii*) pneumonia
• Pneumonia, recurrent[b]
• Progressive multifocal leukoencephalopathy
• Salmonella septicemia, recurrent
• Toxoplasmosis of brain, onset at age >1 month
• Wasting syndrome attributed to HIV[c]

[a] Only among children aged <6 years.

[b] Only among adults, adolescents, and children aged ≥6 years.

[c] Suggested diagnostic criteria for these illnesses, which might be particularly important for HIV encephalopathy and HIV wasting syndrome, are described in the following references:

- 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).
- Centers for Disease Control and Prevention. 1993 Revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. *MMWR*. 1992;41(No. RR-17).

Modified from:

- 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).
- Centers for Disease Control and Prevention: Revised Surveillance Case Definition for HIV Infection—United States, 2014. *MMWR*. 2014;63(No. RR-3):1-10.

Table 7. Antiretroviral Regimens Recommended for Initial Therapy for HIV Infection in Children

An ART regimen for treatment-naive children generally contains one NNRTI **or** one PI boosted with RTV or COBI **or** one INSTI plus a two-NRTI backbone. *Preferred* regimens are designated based on efficacy, ease of administration, and acceptable toxicity. *Alternative* regimens have also demonstrated efficacy, but have more limited experience in children or less favorable ease of administration than *Preferred* regimens. Regimens should be individualized based on the advantages and disadvantages of each combination (see Table 8).

Children who are receiving effective and tolerable ART regimens can continue with those regimens as they age, even if the combinations they are receiving are no longer *Preferred* regimens.

Preferred Regimens		
Age	**Regimens**	**Fixed-Dose Combination Available**
Infants, Birth to Age <14 Days[a,b]	2 NRTIs **plus** NVP	No
	2 NRTIs **plus** RAL	No
Children Aged ≥14 Days to <3 Years	2 NRTIs **plus** LPV/r	No
	2 NRTIs **plus** RAL[c]	No
Children Aged ≥3 Years to <6 Years	2 NRTIs **plus** ATV/r	No
	2 NRTIs **plus** twice-daily DRV/r[d]	No
	2 NRTIs **plus** RAL[c]	No
Children Aged ≥6 Years to <12 Years	2 NRTIs **plus** ATV/r	No
	2 NRTIs **plus** DTG[e]	No
Adolescents Aged ≥12 Years and SMR 1–3	2 NRTIs **plus** ATV/r	No
	2 NRTIs **plus** DTG[e]	FDC available
	2 NRTIs **plus** once-daily DRV/r[d]	No
	2 NRTIs **plus** EVG/COBI[f]	FDCs available
Adolescents Aged ≥12 Years and SMR 4 or 5	Refer to the Adult and Adolescent Guidelines	No
Alternative Regimens		
Age	**Regimens**	**Fixed-Dose Combination Available**
Children Aged >14 Days to <3 Years	2 NRTIs **plus** NVP[g]	No
Children Aged ≥3 Months to <3 Years and Weighing ≥10 kg	2 NRTIs **plus** ATV/r	No

Table 7. Antiretroviral Regimens Recommended for Initial Therapy for HIV Infection in Children, continued

Age	Regimens	Fixed-Dose Combination Available
Children Aged ≥3 Years to <6 Years	2 NRTIs **plus** EFV[h]	No
	2 NRTIs **plus** LPV/r	No
Children Aged ≥6 Years to <12 Years	2 NRTIs **plus** twice-daily DRV/r[d]	No
	2 NRTIs **plus** EFV[h]	No
	2 NRTIs **plus** EVG/COBI[f]	FDCs available
	2 NRTIs **plus** LPV/r	No
	2 NRTIs **plus** RAL[c]	No
Adolescents Aged ≥12 Years and SMR 1–3	2 NRTIs **plus** EFV[h]	FDC available
	2 NRTIs **plus** RAL[c]	No
	2 NRTIs **plus** RPV[i]	FDC available
Preferred 2-NRTI Backbone Options for Use in Combination with Additional Drugs		
Age	**2-NRTI Backbone Options**	**Fixed-Dose Combination Available**
Children, Birth to Age <3 Months	ZDV **plus** (3TC **or** FTC)[j]	No
Children Aged ≥3 Months to <6 Years	ABC **plus** (3TC **or** FTC)[k]	FDC available
	ZDV **plus** (3TC **or** FTC)[j]	FDC available
Children and Adolescents Aged ≥6 Years and SMR 1–3	ABC **plus** (3TC **or** FTC)[k]	FDC available
	FTC/TAF[l]	FDC available
Adolescents Aged ≥12 Years and SMR 4 or 5	Refer to the Adult and Adolescent Guidelines	No
Alternative 2-NRTI Backbone Options for Use in Combination with Additional Drugs		
Age	**2-NRTI Backbone Options**	**Fixed-Dose Combination Available**
Children Aged ≥3 Months	ZDV **plus** ABC	No
Children Aged ≥2 Years to 12 Years	TDF **plus** (3TC **or** FTC)[m]	FDC available
Children and Adolescents Aged ≥6 Years and SMR 1–3	ZDV **plus** (3TC **or** FTC)[j]	FDC available

[a] If treatment is scheduled to begin before a patient is aged 14 days, NVP or RAL are *Preferred* agents because they are the only options with dosing information available for this age group. However, there are currently no clinical trial data suggesting that initiating treatment within the first 14 days of life improves outcome (compared with starting after 14 days of age). Clinicians should consult an expert in pediatric HIV infection. Additional considerations regarding the use of NVP or RAL in infants aged <14 days can be found in Antiretroviral Management of Newborns. A change from NVP to LPV/r should be considered when the infant is aged ≥14 days and 42 weeks postmenstrual age (the span of time between the first day of the mother's last menstrual period and birth, plus the time elapsed after birth), based on infant genotype and better outcomes of LPV/r than NVP in children aged <3 years. Data are very limited on the clinical outcomes of using RAL in infants and children aged <2 years.

[b] LPV/r should not be administered to neonates before a postmenstrual age of 42 weeks and postnatal age ≥14 days.

[c] RAL pills or chewable tablets can be used in children aged ≥2 years. Granules can be administered in infants and children from birth to age 2 years.

[d] DRV once daily should not be used in children aged <12 years or weighing <40 kg. DRV once daily should also not be used if any one of the following resistance-associated substitutions are present: V11I, V32I, L33F, I47V, I50V, I54L, I54M, T74P, L76V, I84V, and L89V. DRV/r is an *Alternative* recommendation for children aged ≥6 years to <12 years because there are options that can be administered once daily. It is *Preferred* for adolescents aged ≥12 years who are not sexually mature (SMR 1–3) where once-daily administration is possible.

[e] DTG is recommended only for children and adolescents weighing ≥30 kg. An FDC tablet containing ABC/DTG/3TC (Triumeq) is available.

[f] EVG is currently recommended only in FDC tablets. Tablets containing EVG/COBI/FTC/TAF are recommended as *Preferred* for children

Table 7. Antiretroviral Regimens Recommended for Initial Therapy for HIV Infection in Children, continued

and adolescents weighing ≥35 kg and as *Alternative* for children aged ≥6 years and weighing ≥25 kg.

[g] NVP should not be used in postpubertal girls with CD4 cell counts >250/mm^3, unless the benefit clearly outweighs the risk. NVP is FDA-approved for treatment of infants aged ≥15 days.

[h] EFV is licensed for use in children aged ≥3 months and weighing ≥3.5 kg, but it is not recommended by the Panel as initial therapy in children aged ≥3 months to 3 years. An FDC tablet containing EFV/FTC/TDF (Atripla) is available.

[i] RPV should be administered to adolescents aged ≥12 years and weighing ≥35 kg who have an initial viral load ≤100,000 copies/mL. FDC tablets containing FTC/RPV/TAF (Odefsey) and FTC/RPV/TDF (Complera) are available.

[j] An FDC containing 3TC/ZDV (Combivir and generic) is available.

[k] An FDC containing ABC/3TC (Epzicom and generic) is available.

[l] An FDC containing FTC/TAF is available. FTC/TAF is FDA-approved for children weighing ≥25 kg when used in the single-tablet regimen EVG/COBI/FTC/TAF or as TAF/FTC in combination with an NNRTI or INSTI. There is insufficient data to recommend use of FTC/TAF in combination with a boosted PI in children weighing <35 kg. For children and adolescents weighing ≥35 kg, TAF can be used in the single-tablet regimen EVG/COBI/FTC/TAF, or as FTC/TAF in combination with an NNRTI, an INSTI, or a boosted PI.

[m] An FDC containing FTC/TDF (Truvada) is available.

Key to Acronyms: 3TC = lamivudine; ABC = abacavir; ATV/r = atazanavir/ritonavir; ART = antiretroviral therapy; CD4 = CD4 T lymphocyte; COBI=cobicistat; DRV = darunavir; DRV/r = darunavir/ritonavir; DTG = dolutegravir; EFV = efavirenz; EVG = elvitegravir; FDA = Food and Drug Administration; FDC = fixed-dose combination; FTC = emtricitabine; INSTI = integrase strand transfer inhibitor; LPV/r = lopinavir/ritonavir; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; NVP = nevirapine; PI = protease inhibitor; RAL = raltegravir; RPV = rilpivirine; SMR = sexual maturity rating; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; ZDV = zidovudine

Table 8. Advantages and Disadvantages of Antiretroviral Components Recommended for Initial Therapy in Children[a] (page 1 of 4)

ARV Class	ARV Agent(s)	Advantages	Disadvantages
INSTIs In Alphabetical Order	All INSTIs	INSTI Class Advantages: • Susceptibility of HIV to a new class of ARV drugs • Few drug-drug interactions • Well-tolerated	INSTI Class Disadvantages: • Limited data on pediatric dosing or safety
	DTG	• Once-daily administration • Can give with food • Available in an FDC tablet containing ABC/DTG/3TC (Triumeq) in a single, but large, tablet • Single-agent DTG pills are available in several dosages and are small in size.	• Drug interactions with EFV, FPV/r, TPV/r, and rifampin, necessitating twice-daily dosing • CNS side effects, particularly sleep disturbances
	EVG	• Once-daily administration • Available in the following FDC tablets: EVG/COBI/FTC/TDF (Stribild) and EVG/COBI/FTC/TAF (Genvoya)	• COBI has the potential for multiple drug interactions because of metabolism via hepatic enzymes (e.g., CYP3A4). • COBI inhibits tubular secretion of creatinine and may result in increased serum creatinine but normal glomerular clearance.
	RAL	• Can give with food • Available in tablet, chewable tablet, and powder formulations • Once-daily administration (with RAL HD) can be used for treatment-naive or virologically suppressed children weighing ≥50 kg.	• Potential for rare systemic allergic reaction or hepatitis • Powder formulation requires a multistep preparation before administration.

Table 8. Advantages and Disadvantages of Antiretroviral Components Recommended for Initial Therapy in Children[a] (page 2 of 4)

ARV Class	ARV Agent(s)	Advantages	Disadvantages
NNRTIs In Alphabetical Order	All NNRTIs	NNRTI Class Advantages: • Long half-life • 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 NVP) • Potential for multiple drug interactions due to metabolism via hepatic enzymes (e.g., CYP3A4)
	EFV	• Once-daily administration • Available in the FDC EFV/FTC/TDF (Atripla) • Potent ARV activity • Can give with food (but avoid high-fat meals) • Capsules can be opened and added to food	• Neuropsychiatric AEs (bedtime dosing recommended to reduce CNS effects) • Rash (generally mild) • No commercially available liquid • Limited data on dosing for children aged <3 years • No data on dosing for children aged <3 months
	NVP	• Liquid formulation available • Dosing information for young infants available • Can give with food • Extended-release formulation is available that allows for once-daily dosing in older children.	• Reduced virologic efficacy in young infants, regardless of exposure to NVP as part of a peripartum preventive regimen • Higher incidence of rash/HSR than other NNRTIs • Higher rates of serious hepatic toxicity than EFV • Decreased virologic response compared with EFV • Twice-daily dosing necessary in children with BSA <0.58 m^2
	RPV	• Once-daily dosing • Available in the following 1-pill-daily, FDC tablets: FTC/RPV/TDF (Complera) and FTC/RPV/TAF (Odefsey)	• Should not use in patients with HIV viral load >100,000 copies/mL • Low barrier for resistance
PIs In Alphabetical Order	All PIs	PI Class Advantages: • NNRTI-sparing • Clinical, virologic, and immunologic efficacy are well-documented. • Resistance to PIs requires multiple mutations • When combined with a dual-NRTI backbone, a regimen containing a PI targets HIV at 2 steps of viral replication by inhibiting the activity of 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 • Most PIs require RTV boosting, resulting in associated drug interactions.

Table 8. Advantages and Disadvantages of Antiretroviral Components Recommended for Initial Therapy in Children[a] (page 3 of 4)

ARV Class	ARV Agent(s)	Advantages	Disadvantages
PIs In Alphabetical Order, continued	Boosted ATV	• Once-daily dosing • Powder formulation available • ATV has less effect on TG and total cholesterol levels than other PIs (but RTV boosting may be associated with elevations in these parameters). • ATV requires a boosting agent. ATV/COBI is available as an FDC tablet (Evotaz), which can reduce the pill burden associated with a boosted-PI regimen. However, the use of ATV/COBI in pediatric patients is still being investigated. RTV is currently the only boosting agent for ATV that is FDA-approved for use in children.	• No liquid formulation • Food effect (should be administered with food) • Indirect hyperbilirubinemia is common, but asymptomatic • Must be used with caution in patients with preexisting conduction system defects (can prolong PR interval of ECG) • RTV component associated with a large number of drug interactions
	Boosted DRV	• Can be used once daily in children aged ≥12 years • Liquid formulation available • DRV requires a boosting agent. DRV/COBI is available as an FDC tablet (Prezcobix), which can reduce the pill burden associated with a boosted-PI regimen. However, the use of DRV/COBI in pediatric patients is still being investigated. RTV is currently the only boosting agent for DRV that is FDA-approved for use in children.	• Pediatric pill burden high with current tablet dose formulations • Food effect (should be administered with food) • Must be boosted to achieve adequate plasma concentrations • Contains sulfa moiety. The potential for cross sensitivity between DRV and other drugs in sulfonamide class is unknown. • RTV component associated with a large number of drug interactions • Can only be used once daily in the absence of certain PI-associated resistance mutations
	LPV/r	• LPV only available coformulated with RTV in 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 is better than RTV alone • Food effect (liquid formulation should be administered with food) • RTV component is associated with large number of drug interactions • Should not be administered to neonates before a postmenstrual age (the span of time between the first day of the mother's last menstrual period and birth, plus the time elapsed after birth) of 42 weeks and a postnatal age ≥14 days • Must be used with caution in patients with pre-existing conduction system defects (can prolong PR and QT interval of ECG)
Dual-NRTI Backbones In Alphabetical Order	ABC **plus** (3TC **or** FTC)	• Palatable liquid formulations • Can give with food. • ABC and 3TC are available in the following FDC tablets: ABC/3TC (Epzicom and generic; for older/larger patients) and ABC/DTG/3TC (Triumeq; a single, large tablet).	• Risk of ABC HSR; perform HLA-B*5701 screening before initiation of ABC treatment.
	FTC/TAF for children aged ≥6 years	• Once-daily dosing • Small tablet size • Less TFV-associated renal and bone toxicity with TAF compared to TDF in adults • FTC and TAF are available in the following FDC tablets: FTC/TAF (Descovy), EVG/COBI/FTC/TAF (Genvoya), and FTC/RPV/TAF (Odefsey)	• Limited data in children • Increased lipids

Table 8. Advantages and Disadvantages of Antiretroviral Components Recommended for Initial Therapy in Children[a] (page 4 of 4)

ARV Class	ARV Agent(s)	Advantages	Disadvantages
Dual-NRTI Backbones In Alphabetical Order, continued	TDF **plus** (3TC **or** FTC) for adolescents with SMR 4 or 5	• Once-daily dosing for TDF • Resistance is slow to develop • Less mitochondrial toxicity than other NRTIs • Can give with food • Available as reduced-strength tablets and oral powder for use in younger children • FTC and TDF are available in the following FDC tablets: FTC/TDF (Truvada; available in multiple dosages), EFV/FTC/TDF (Atripla), EVG/COBI/FTC/TDF (Stribild), and FTC/RPV/TDF (Complera)	• Limited pediatric experience • Potential bone and renal toxicity; toxicity may be less in post-pubertal children • Appropriate dosing is complicated by numerous drug-drug interactions with other ARV agents, including ddI, LPV/r, ATV, and TPV.
	ZDV **plus** (3TC **or** FTC)	• Extensive pediatric experience • ZDV and 3TC are coformulated as single pill (Combivir and generic) 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
	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

[a] See Appendix A: Pediatric Antiretroviral Drug Information and Table 7. Antiretroviral Regimen Considerations as Initial Therapy based on Specific Clinical Scenarios in the Adult and Adolescent Guidelines for more information.

Key to Acronyms: 3TC = lamivudine; ABC = abacavir; AE = adverse event; ARV = antiretroviral; ATV = atazanavir; BSA = body surface area; CNS = central nervous system; COBI = cobicistat; CYP = cytochrome P; ddI = didanosine; DRV = darunavir; DTG = dolutegravir; ECG = electrocardiogram; EFV = efavirenz; EVG = elvitegravir; FDC = fixed-dose combination; FPV/r = fosamprenavir/ritonavir; FTC = emtricitabine; HSR = hypersensitivity reaction; INSTI = integrase strand transfer inhibitor; LPV = lopinavir; LPV/r = lopinavir/ritonavir; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; NVP = nevirapine; PI = protease inhibitor; PK = pharmacokinetic; RAL = raltegravir; RPV = rilpivirine; RTV = ritonavir; SJS = Stevens-Johnson Syndrome; SMR = sexual maturity rating; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; TFV= tenofovir; TG = triglycerides; TPV = tipranavir; TPV/r = tipranavir/ritonavir; ZDV = zidovudine

Table 9. Antiretroviral Regimens or Components Not Recommended for Initial Treatment of HIV Infection in Children

Regimen or ARV Component	Rationale
Unboosted **ATV**-containing regimens in children	Reduced exposure
DRV-based regimens once daily in children aged ≥3 to 12 years	Insufficient data to recommend
Unboosted **DRV**	Use without ritonavir has not been studied
Dual (full-dose) PI regimens	Insufficient data to recommend Potential for added toxicities
Dual-NRTI combination of **ABC plus TDF**	Insufficient data to recommend
EFV-based regimens for children aged <3 years	Appropriate dose not determined
T-20-containing regimens	Insufficient data to recommend Injectable preparation
ETR-based regimens	Insufficient data to recommend
FPV-based regimens	Reduced exposure Medication burden
IDV-based regimens	Renal toxicities
LPV/r dosed once daily	Reduced drug exposure
MVC-based regimens	Insufficient data to recommend
NFV-based regimens	Variable PK Appropriate dose not determined in young infants
Regimens containing only NRTIs	Inferior virologic efficacy
Regimens containing 3 drug classes	Insufficient data to recommend
Full-dose **RTV** or use of **RTV** as the sole PI	GI intolerance Metabolic toxicity
Regimens containing 3 NRTIs and 1 NNRTI	Added cost and complexity outweighs any benefit
SQV-based regimens	Limited dosing and outcome data
TDF-containing regimens in children aged <2 years	Potential bone toxicity Appropriate dose has yet to be determined
TPV-based regimens	Increased dose of RTV for boosting Reported cases of intracranial hemorrhage

Key to Acronyms: ABC = abacavir; ARV = antiretroviral; ATV = atazanavir; DRV = darunavir; EFV = efavirenz; ETR = etravirine; FPV = fosamprenavir; GI = gastrointestinal; IDV = indinavir; LPV/r = lopinavir/ritonavir; MVC = maraviroc; NFV = nelfinavir; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; PK = pharmacokinetics; RTV = ritonavir; SQV = saquinavir; T-20 = enfuvirtide; TDF = tenofovir disoproxil fumarate; TPV = tipranavir

Table 10. ART Regimens or Components Never Recommended for Treatment of HIV Infection in Children

ART Regimens Never Recommended for Children		
Regimen	**Rationale**	**Exceptions**
1 ARV Drug Alone (Monotherapy)	• Rapid development of resistance • Inferior antiviral activity compared to combinations that include ≥3 ARV drugs • Monotherapy "holding" regimens are associated with more rapid CD4 declines than non-suppressive ART	• Infants with perinatal HIV exposure and negative virologic tests who are receiving 4 to 6 weeks of ZDV prophylaxis to prevent perinatal transmission of HIV
2 NRTIs Alone	• Rapid development of resistance • Inferior antiviral activity compared to combinations that include ≥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 was 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 was used as initial therapy in treatment-naive adults	• No exceptions
ARV Components Never Recommended as Part of an ARV Regimen for Children		
Regimen	**Rationale**	**Exceptions**
ddI and d4T, Individually or Co-Administered	• Increased toxicities • ddI plus d4T is **contraindicated**	• No exceptions
ATV plus IDV	• Potential additive hyperbilirubinemia	• No exceptions
Dual-NNRTI Combinations	• Enhanced toxicity	• No exceptions
Dual-NRTI Combinations: **• 3TC plus FTC**	• Similar resistance profile and no additive benefit	• No exceptions
• d4T plus ZDV	• Antagonistic effect on HIV	• No exceptions
NVP as Initial Therapy in Adolescent Girls with CD4 Counts >250 cells/mm^3 or Adolescent Boys with CD4 Counts >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 bioavailability • Inferior virologic activity compared with other PIs	• No exceptions

Key to Acronyms: 3TC = lamivudine; ABC = abacavir; ART = antiretroviral therapy; ARV = antiretroviral; ATV = atazanavir; CD4 = CD4 T lymphocyte; d4T = stavudine; ddI = didanosine; DRV = darunavir; FTC = emtricitabine; IDV = indinavir; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; NVP = nevirapine; SQV = saquinavir; TDF = tenofovir disoproxil fumarate; TPV = tipranavir; ZDV = zidovudine

Table 11. Newborn Antiretroviral Management According to Risk of HIV Infection in the Newborn

Drug selection and dosing considerations are related to the age and gestational age of the newborn. Consultation is available through the National Perinatal HIV Hotline (888-448-8765).

Category	Description	Neonatal ARV Management
Low Risk of Perinatal HIV Transmission	Mothers received standard ART during pregnancy with sustained viral suppression near delivery and no concerns related to adherence	4 weeks of ZDV
Higher Risk of Perinatal HIV Transmission[a,b]	• Mothers who received neither antepartum nor intrapartum ARV drugs • Mothers who received only intrapartum ARV drugs • Mothers who received antepartum and intrapartum ARV drugs but who have detectable viral load near delivery, particularly if delivery was vaginal • Mothers with acute or primary HIV infection during pregnancy or breastfeeding[c]	Combination ARV prophylaxis with 6 weeks ZDV and 3 doses of NVP (prophylaxis dosage, with doses given within 48 hours of birth, 48 hours after first dose, and 96 hours after second dose) or Empiric HIV therapy consisting of ZDV, 3TC, and NVP (treatment dosage)[d]
Presumed Newborn HIV Exposure	Mothers with unknown HIV status who test positive at delivery or postpartum or whose newborns have a positive HIV antibody test	ARV management as above (for higher risk of perinatal HIV transmission). ARV management should be discontinued immediately if supplemental testing confirms that mother does not have HIV.
Newborn with Confirmed HIV[e]	Confirmed positive newborn HIV virologic test/NAT	3 drug combination ARV regimen at treatment dosage

[a] See text for evidence supporting combination ARV prophylaxis and empiric HIV therapy.

[b] See the Intrapartum Care section for guidance on indications for scheduled cesarean delivery and intrapartum IV ZDV to reduce the risk of perinatal HIV transmission for mothers with elevated viral load at delivery.

[c] Most experts would opt to administer empiric HIV therapy to infants with acute HIV during pregnancy because of the high risk for *in utero* infection. If acute HIV is diagnosed during breastfeeding, mother should stop breastfeeding.

[d] The optimal duration of empiric HIV therapy in newborns at higher risk of perinatal HIV transmission is unknown. Many experts administer 6 weeks of combination therapy; others opt to discontinue NVP and/or 3TC after the return of negative newborn testing. ZDV should be continued for 6 weeks.

[e] Most experts do not recommend delaying the initiation of ART while waiting for the results of the confirmatory HIV NAT, given low likelihood of false-positive HIV NAT testing.

Note: ARV drugs should be initiated as close to the time of birth as possible, preferably within 6 to 12 hours of delivery. See Table 8 for dosing specifics.

Key to Acronyms: 3TC = lamivudine; ART = antiretroviral therapy; ARV =antiretroviral; IV = intravenous; NAT = nucleic acid test; NVP = nevirapine; ZDV = zidovudine

Table 12. Newborn Antiretroviral Dosing Recommendations

<table>
<tr><th>Drug</th><th>Dosing</th></tr>
<tr><td rowspan="3">ZDV
Treatment and Prophylaxis Dosage

Note: For newborns unable to tolerate oral agents, the IV dose is 75% of the oral dose while maintaining the same dosing interval.</td><td>≥35 Weeks' Gestation at Birth
Birth to Age 4–6 Weeks:
• 4 mg/kg/dose orally twice daily

Simplified Weight-Band Dosing for Newborns ≥35 Weeks:
<table>
<tr><th>Weight Band (kg)</th><th>* Volume (mL)
ZDV 10 mg/mL Oral Syrup
Twice Daily</th></tr>
<tr><td>2 to <3 kg</td><td>1 mL</td></tr>
<tr><td>3 to <4 kg</td><td>1.5 mL</td></tr>
<tr><td>4 to <5 kg</td><td>2 mL</td></tr>
</table></td></tr>
<tr><td>≥30 to <35 Weeks' Gestation at Birth
Birth–Age 2 Weeks:
• 2 mg/kg/dose orally twice daily

Age 2 Weeks to 4–6 Weeks:
• 3 mg/kg/dose orally twice daily</td></tr>
<tr><td><30 weeks' Gestation at Birth
Birth–Age 4 Weeks:
• 2 mg/kg/dose orally twice daily

Age 4–6 Weeks:
• 3 mg/kg/dose orally twice daily</td></tr>
<tr><td>3TC
Treatment and Prophylaxis Dosage</td><td>≥32 Weeks' Gestation at Birth:
Birth–Age 4 Weeks:
• 2 mg/kg/dose orally twice daily

Age 4–6 Weeks:
• 4 mg/kg/dose orally twice daily</td></tr>
<tr><td>NVP
Prophylaxis Dosage</td><td>≥32 Weeks Gestation at Birth:
3 doses given (1) within 48 hours of birth, (2) 48 hours after the 1st dose, and (3) 96 hours after the 2nd dose

Birth Weight 1.5–2 kg:
• 8-mg dose orally
• Note: No calculation is required for this dose; this is the actual dose, not a mg/kg dose.

Birth Weight >2 kg:
• 12-mg dose orally
• Note: No calculation is required for this dose; this is the actual dose, not a mg/kg dose.</td></tr>
<tr><td>NVP
Treatment Dosage</td><td>≥37 Weeks' Gestation at Birth
Birth–Age 6 Weeks:
• 6 mg/kg/dose orally twice daily

34 to <37 Weeks' Gestation at Birth
Birth–Age 1 Week:
• 4 mg/kg/dose orally twice daily

Age 1–6 Weeks:
• 6 mg/kg/dose orally twice daily</td></tr>
</table>

Key to Acronyms: 3TC=lamivudine; IV= intravenous; NVP = nevirapine; ZDV = zidovudine

Table 13. Evidence-Based Approaches for Monitoring Medication Adherence

Routine Assessment of Medication Adherence in Clinical Care[a]	Description
Monitor viral load.	Viral load monitoring should be done more frequently after initiating or changing medications.[a]
Assess quantitative self-report of missed doses.	Ask patient and/or caregiver about the number of missed doses over defined period (1, 3, or 7 days).
Elicit description of medication regimen.	Ask patient and/or caregiver about the name/appearance, number, frequency of medications.
Assess barriers to medication administration.	Engage the patient and caregiver in dialogue around facilitators and challenges to adherence.
Monitor pharmacy refills.	Approaches include pharmacy-based or clinic-based assessment of on-time medication refills.
Conduct announced and unannounced pill counts.	Approaches include asking patients to bring medications to clinic or home visits, or referral to community health nursing.
Targeted Approaches to Monitor Adherence in Special Circumstances	**Description**
Implement DOT.	Include brief hospitalization if indicated.
Measure plasma drug concentration.	Can be considered for particular drugs.[b]
Approaches to Monitor Medication Adherence in Research Settings	**Description**
Measure drug concentrations in hair.	Good measure of adherence over time.[c]
Use electronic monitoring devices.	MEMS caps, Wisepill
Use mobile phone-based technologies.	Interactive voice response, SMS text messaging, mobile apps

[a] See Clinical and Laboratory Monitoring After Initiation of Combination Antiretroviral Therapy (or After a Change in Combination Antiretroviral Therapy) regarding the frequency of adherence assessment after initiating or changing therapy.

[b] See Role of Therapeutic Drug Monitoring in Management of Pediatric HIV Infection regarding indications for therapeutic drug monitoring.

[c] Sources:
Olds PK, Kiwanuka JP, Nansera D, et al. Assessment of HIV antiretroviral therapy adherence by measuring drug concentrations in hair among children in rural Uganda. *AIDS Care*. 2015;27(3):327-332. Available at https://www.ncbi.nlm.nih.gov/pubmed/25483955.[48]

Chawana TD, Gandhi M, Nathoo K, et al. defining a cutoff for atazanavir in hair samples associated with virological failure among adolescents failing second-line antiretroviral treatment. *J Acquir Immune Defic Syndr*. 2017;76(1):55-59. Available at https://www.ncbi.nlm.nih.gov/pubmed/28520618.[49]

Pintye J, Bacchetti P, Teeraananchai S, et al. brief report: lopinavir hair concentrations are the strongest predictor of viremia in HIV-infected Asian children and Aadolescents on second-line antiretroviral therapy. *J Acquir Immune Defic Syndr*. 2017. Available at https://www.ncbi.nlm.nih.gov/pubmed/28825944.[18]

Key to Acronyms: apps = applications; DOT = directly observed therapy; MEMS = Medication Event Monitoring System

Table 14. Strategies to Improve Adherence to Antiretroviral Medications

Initial Intervention Strategies
• Establish trust and identify mutually acceptable goals for care.
• Obtain explicit agreement on the need for treatment and adherence.
• Identify depression, low self-esteem, substance abuse, or other mental health issues in the child/adolescent and/or caregiver that may decrease adherence. Evaluate and initiate treatment for mental health issues before starting ARV drugs, if possible.
• Identify family, friends, health team members, and others who can support adherence.
• Educate patient and family about the critical role of adherence in therapy outcome, including the relationship between partial adherence and resistance and potential impact on future drug regimen choices. Develop a treatment plan that the patient and family understand and to which they feel committed.
• Work with the patient and family to make specific plans for taking medications as prescribed and supporting adherence. Assist them to arrange for administration in day care, school, and other settings, when needed. Consider home delivery of medications.
• Establish readiness to take medication through practice sessions or other means.
• Schedule a home visit to review medications and determine how they will be administered in the home setting.
• In certain circumstances, consider a brief period of hospitalization at the start of therapy for patient education and to assess tolerability of medications chosen.
Medication Strategies
• Choose the simplest regimen possible, reducing dosing frequency, pill size, and number of pills.
• When choosing a regimen, consider 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 AEs; provide anticipatory guidance for management of AEs.
• Simplify food requirements for medication administration.
• Prescribe drugs carefully to avoid adverse drug-drug interactions.
• Assess pill-swallowing capacity and offer pill-swallowing training and aids (e.g., pill-swallowing cup, pill glide). Adjust pill size as needed.
Follow-up Intervention Strategies
• Have more than one member of the multidisciplinary team monitor adherence at each visit and in between visits by telephone, email, text, and social media, as needed.
• Provide ongoing support, encouragement, and understanding of the difficulties associated with maintaining adherence to daily medication regimens.
• Use patient education aids including pictures, calendars, and stickers.
• Encourage use of pill boxes, reminders, mobile apps, alarms, 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, blister packs, refill reminders, automatic refills, and home delivery of medications.
• Consider DOT at home, in the clinic, or in certain circumstances, such as during a brief inpatient hospitalization.
• Consider gastrostomy tube use in certain circumstances.
• Information on other interventions to consider can be found at the Complete Listing of Medication Adherence Evidence-Based Behavioral Interventions.
• Consult the CDC Every Dose Every Day toolkit

Key to Acronyms: apps = applications; ARV = antiretroviral; AE = adverse effect; DOT = directly observed therapy

Table 15a. Antiretroviral-Therapy-Associated Adverse Effects and Management Recommendations—Central Nervous System Toxicity (Last updated May 22, 2018; last reviewed May 22, 2018) (page 1 of 3)

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/Premature Infants:* • Global CNS depression (e.g., abnormal EEG, altered state of consciousness, somnolence)	Unknown, rare case reports	Prematurity Low birth weight Aged <14 days (whether premature or term)	Avoid use of LPV/r until a postmenstrual age of 42 weeks and a postnatal age ≥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 (i.e., postmenstrual age of 42 weeks and a postnatal age ≥14 days).
Neuropsychiatric Symptoms and Other CNS Manifestations	EFV	Onset: • For many symptoms, onset is 1–2 days after starting EFV • Many symptoms subside or diminish by 2–4 weeks, but may persist in a significant proportion of patients. In one report, 37% of participants experienced persistent symptoms at 12 months and in another report, half of discontinuations occurred after 12 months. Presentation (May Include 1 or More of the Following) *Neuropsychiatric Symptoms:* • Abnormal dreams • Psychosis • Suicidal ideation or attempted/ completed suicide *Other CNS Manifestations:* • Dizziness • Somnolence • Insomnia or poor sleep quality • Impaired concentration • Seizures (including absence seizures)	Variable, depending on age, symptom, and assessment method Children: • 24% for any EFV-related CNS manifestations in 1 case series, with 18% of participants requiring drug discontinuation. • 11% (5/45 participants) incidence of new-onset seizures reported in 1 study in children aged <36 months, 2 of whom had alternative causes for seizures. • Cases of cerebellar dysfunction have been reported in children in association with very high EFV plasma levels. Adults: • 30% incidence for any CNS manifestations of any severity. • 6% incidence for EFV-related severe CNS manifestations, including suicidality. However, evidence is conflicting about whether EFV use increases the incidence of suicidality.	Insomnia associated with elevated EFV trough concentration ≥4 mcg/mL Presence of CYP450 polymorphisms that decrease EFV metabolism and cause increased EFV serum concentrations (CYP2B6 516 TT genotype or co-carriage of CYP2B6 516 G/T and 983 T/C variants) Prior history of psychiatric illness or use of psychoactive drugs	Administer EFV on an empty stomach, preferably at bedtime. Prescreen for and avoid use in the presence of psychiatric illness, including depression or suicidal thoughts. Avoid concomitant use of psychoactive drugs. TDM can be considered in the context of a child with mild or moderate EFV-associated toxicity..	If symptoms are excessive or persistent, obtain EFV trough concentration. If EFV trough concentration >4 mcg/mL and/or symptoms are severe, strongly consider drug substitution if suitable alternative exists. Alternatively, consider dose reduction with repeat TDM and dose adjustment (with expert pharmacologist input).

Table 15a. Antiretroviral-Therapy-Associated Adverse Effects and Management Recommendations—Central Nervous System Toxicity (Last updated May 22, 2018; last reviewed May 22, 2018) (page 2 of 3)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
Neuropsychiatric Symptoms and Other CNS Manifestations, continued	EFV, continued	• Cerebellar dysfunction (tremor, dysmetria, ataxia) **Note:** CNS side effects such as impaired concentration, abnormal dreams, or sleep disturbances may be more difficult to assess in children.	• 1 case series reported 20 women with ataxia which resolved upon EFV discontinuation, but frequency was not reported.			
	RPV	Onset: • Most symptoms occur in the first 4–8 weeks of treatment Presentation *Neuropsychiatric Symptoms:* • Depressive disorders • Suicidal ideation • Abnormal dreams/nightmares *Other CNS Manifestations:* • Headache • Dizziness • Insomnia • Somnolence	Adults: • CNS/neuro-psychiatric adverse events of all severity grades were reported in 43% of patients at 96 weeks (mostly Grade 1). Depressive disorders of all severity grades were reported in 9% of patients, and were severe, requiring RPV discontinuation in 1% of patients. Children: • Depressive disorders of all severity grades were reported in 19.4% of pediatric patients aged 12–17 years. Severe depressive disorders were reported in 5.6% of patients, including 1 suicide attempt. • Somnolence reported in 14% (5/36) of children.	Prior history of neuropsychiatric illness	Monitor carefully for depressive disorders and other CNS symptoms.	Consider drug substitution in cases of severe symptoms.
	RAL	Onset: • As early as 3–4 days after starting RAL Presentation: • Increased psychomotor activity • Headaches • Insomnia • Depression • Cerebellar dysfunction (e.g., tremor, dysarthria, ataxia)	Children: • Increased psychomotor activity reported in 1 child. Adults: • Headache • Insomnia (<5% in adult trials) • Rare case reports of cerebellar dysfunction in adults	Elevated RAL concentrations Co-treatment with TDF or PPI or inhibitors of UGT1A1 Prior history of insomnia or depression	Prescreen for psychiatric symptoms. Monitor carefully for CNS symptoms. Use with caution in the presence of drugs that increase RAL concentration.	Consider drug substitution (RAL or co-administered drug) in cases of severe insomnia or other neuropsychiatric symptoms.

Table 15a. Antiretroviral-Therapy-Associated Adverse Effects and Management Recommendations—Central Nervous System Toxicity (Last updated May 22, 2018; last reviewed May 22, 2018) (page 3 of 3)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
Neuropsychiatric Symptoms and Other CNS Manifestations, continued	DTG	Onset: • 7–30 days after starting DTG Presentation *Neuropsychiatric Symptoms:* • Depression or exacerbation of preexisting depression • Anxiety • Suicidal ideation or attempted/ completed suicide *Other CNS Manifestations (Generally Mild):* • Insomnia • Dizziness • Headache	Children: • CNS symptoms were uncommonly reported in early clinical experience in children and adolescents. Adults: • Exact frequency of neuropsychiatric symptoms is unknown; case reports of 4 adult patients. Headache, insomnia, and dizziness are common and usually mild. More severe symptoms that require drug discontinuation are less common, occurring in <1% patients in Phase 3 trials, but these severe symptoms are reported with increasing frequency (4% to 10%) in recent post-marketing reports.	Pre-existing depression or other psychiatric illness Higher frequency of neuropsychiatric symptoms reported when co-administered with ABC	Use with caution in the presence of psychiatric illness, especially depression.	For severe neuropsychiatric symptoms, consider discontinuation of DTG if suitable alternative exists. Discontinuation resulted in resolution of neuropsychiatric symptoms in 3 out of 4 patients (in the fourth patient, symptoms resolved slowly despite DTG continuation). For mild symptoms, continue DTG and counsel patient that symptoms will likely resolve with time.
Intracranial Hemorrhage (ICH)	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 py or 0.04–0.22/100 py in a retrospective review of 2 large patient databases.	Unknown; prior history of bleeding disorder or risk factors for bleeding reported for most patients in case series.	Administer TPV with caution in patients with bleeding disorder, known intracranial lesions, or recent neurosurgery.	Discontinue TPV if ICH is suspected or confirmed.

Key to Acronyms: ABC = abacavir; ARV = antiretroviral; CNS = central nervous system; CYP = cytochrome P; DTG = dolutegravir; EEG = electroencephalogram; EFV = efavirenz; ICH = intracranial hemorrhage; LPV/r = lopinavir/ritonavir; PPI = proton pump inhibitor; py = patient years; RAL = raltegravir; RPV = rilpivirine; TDF = tenofovir disoproxil fumarate; TDM = therapeutic drug monitoring; TPV = tipranavir; UGT = uridine diphosphate-glucurononyl transferase

Table 15b. Antiretroviral-Therapy-Associated Adverse Effects and Management Recommendations—Dyslipidemia

(Last updated May 22, 2018; last reviewed May 22, 2018) (page 1 of 2)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/Monitoring	Management
Dyslipidemia	PIs: • All PIs, especially RTV-boosted PIs; lower incidence reported with DRV/r and ATV with or without RTV. NRTIs: • Especially d4T[e] • Lower incidence reported with TDF than TAF NNRTIs: • Lower incidence reported with NVP, RVP, and ETR than EFV	Onset: • As early as 2 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	Reported frequency varies with specific ARV regimen, duration of ART, and specific laboratory parameters used to diagnose lipid abnormalities. 10% to 20% in young children receiving LPV/r. 40% to 75% of older children and adolescents with prolonged ART history will have lipid abnormalities. Higher abnormal fasting serum lipids in EVG/COBI/FTC/TAF vs. EVG/COBI/FTC/TDF regimen in studies of treatment- naive adults. Increase in serum lipids from baseline also noted in adolescents receiving EVG/COBI/FTC/TAF.	Advanced-stage HIV disease High-fat, high-cholesterol diet Lack of exercise Obesity Hypertension Smoking Family history of dyslipidemia or premature CVD Metabolic syndrome Fat maldistribution	Prevention: • Low-fat diet • Exercise • Smoking-prevention counseling • Do not use d4T Monitoring[a] *Adolescents and Adults:* • Monitor 12-hour FLP, which includes TC, HDL-C, non-HDL-C, LDL-C, and TG, every 6–12 months. Obtain FLPs twice (>2 weeks but ≤3 months apart, average results) before initiating or changing lipid-lowering therapy. *Children (Aged ≥2 Years) without Lipid Abnormalities or Additional Risk Factors:* • Obtain nonfasting screening lipid profiles at entry into care and then, if levels are normal, 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 12-hour FLP before initiating or changing therapy and every 6 months thereafter (more often if indicated). *Children Receiving Lipid-Lowering Therapy with Statins or Fibrates:* • Obtain 12-hour FLP, LFTs, and CK at 4 and 8 weeks, and 3 months after starting lipid therapy.	Assessment of additional CVD risk factors should be done in all patients. Patients living with HIV are considered to be at moderate risk of CVD.[b] Counsel on lifestyle modification and dietary interventions (e.g., a diet low in saturated fat, cholesterol, and refined sugars, particularly in cases of ↑TG, elimination of trans fat in the diet, increase in physical activity, smoking cessation) for an adequate trial period (3–6 months). Consider consultation with dietician. ART regimen changes can be considered. Discontinue d4T or substitute a PI-sparing regimen or PI-based regimen with a more favorable lipid profile. Consider lipid-lowering therapy in consultation with a lipid specialist if ≥6-month trial of lifestyle modification fails. Some experts suggest treating children receiving ARV drugs according to NHLBI cardiovascular risk reduction guidelines for children aged ≥10 years: LDL-C ≥190 mg/dL, regardless of additional risk factors; LDL-C ≥160 mg/dL or LDL-C ≥130 mg/dL based on presence of additional risk factors and risk conditions.[b] The minimal goal of therapy should be to achieve and maintain a LDL-C value below 130 mg/dL, while minimizing side effects and maintaining viral control.

Table 15b. Antiretroviral-Therapy-Associated Adverse Effects and Management Recommendations—Dyslipidemia

(Last updated May 22, 2018; last reviewed May 22, 2018) (page 2 of 2)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/Monitoring	Management
Dyslipidemia					• If minimal alterations in AST, ALT, and CK, monitor every 3–4 months in the first year and every 6 months thereafter (or as clinically indicated). • Repeat FLPs 4 weeks after increasing doses of antihyperlipidemic agents.	Statins such as pravastatin, atorvastatin, or rosuvastatin[c] can be considered.[d] Pravastatin has lower lipid-lowering potency compared to other statins. Statin-induced lipid lowering effect appears more pronounced than ARV substitution. Statin-related toxicities include liver enzyme elevation and myopathy, and risk may be increased by drug interactions with ART, particularly PIs.[c] Statins may also increase the risk of insulin resistance and type 2 diabetes mellitus, but data are conflicting. Risks must be weighed against potential benefits. Cholesterol absorption inhibitors (e.g., ezetimibe) can be considered as alternatives. Drug therapy for severe hypertriglyceridemia (TG ≥500 mg/dL) can be considered. Fibrates (gemfibrozil and fenofibrate) and N-3 PUFAs derived from fish oils may be used. The long-term risks of lipid abnormalities in children receiving ART are unclear. However, persistent dyslipidemia in children may lead to premature CVD.

[a] Given the burden of collecting fasting blood samples, some practitioners routinely measure cholesterol and triglycerides from nonfasting blood samples and follow up abnormal values with a test done in the fasted state.

[b] Refer to NHLBI guidelines at https://www.nhlbi.nih.gov/sites/default/files/media/docs/peds_guidelines_full.pdf.

[c] 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.

[d] Statins (HMG-CoA reductase inhibitors) are contraindicated in pregnancy (due to being potentially teratogenic) and should not be used in patients who may become pregnant. Multiple drug interactions exist between ARV drugs and statins (except for pravastatin, which is not dependent on CYP3A4 for metabolism). Pravastatin, atorvastatin, rosuvastatin (Crestor®), fluvastatin, and ezetimibe (Zetia®) are approved for use in children aged ≥10 years. For additional information, see the PI, NNRTI, NRTI, and INSTI Drug Interactions Tables in the Adult and Adolescent Guidelines.

[e] d4T is no longer recommended for use in an ARV regimen

Key to Acronyms: ALT = alanine aminotransferase; ART = antiretroviral therapy; ARV = antiretroviral; AST = aspartate aminotransferase; ATV = atazanavir; CK = creatine kinase; COBI = cobicistat; CVD = cardiovascular disease; CYP3A4 = cytochrome P450 3A4; d4T = stavudine; DRV/r = darunavir/ritonavir; EFV = efavirenz; ETR = etravirine; EVG = elvitegravir; FLP = fasting lipid profile; FTC = emtricitabine; HDL-C = high-density lipoprotein cholesterol; INSTI = integrase strand transfer inhibitor; LDL-C = low-density lipoprotein cholesterol; LFT = liver function test; LPV = lopinavir; LPV/r = lopinavir/ritonavir; NHLBI = National Heart, Lung, and Blood Institute; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; NVP = nevirapine; PI = protease inhibitor; PUFA = polyunsaturated fatty acid; RPV = rilpivirine; RTV = ritonavir; TAF = tenofovir alafenamide; TC = total cholesterol; TDF = tenofovir disoproxil fumarate; TG = triglyceride

Table 15c. Antiretroviral-Therapy-Associated Adverse Effects and Management Recommendations—Gastrointestinal Effects (Last updated May 22, 2018; last reviewed May 22, 2018) (page 1 of 2)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/Monitoring	Management
Nausea/ Vomiting	All ARVs, but most notably— NRTIs: • ddI and ZDV at a higher rate than others PIs: • Especially with RTV boosting (e.g., LPV/r, DRV/r)	Onset: • Early Presentation: • Nausea, emesis—may be associated with anorexia and/or abdominal pain	Varies with ARV agent; 10% to 30% in some series	Unknown	Instruct patient to take PIs with food. Monitor for weight loss, ARV adherence. **Do not use** ddI, d4T, or NFV (individually or together) as part of an ARV regimen.[a]	Reassure patient that these adverse effects generally improve over time (usually 6–8 weeks). Supportive care. In extreme or persistent cases, use antiemetics or switch ARV regimen.
Diarrhea	PIs: • Particularly NFV, LPV/r, and DRV/r NRTIs: • ddI and d4T at a higher rate than 3TC or FTC	Onset: • Early Presentation: • Generally soft, more frequent stools	Varies with ARV agent; generally <15% (range 5% to 30%)	Unknown	Monitor for weight loss, dehydration. **Do not use** ddI, d4T, or NFV (individually or together) as part of an ARV regimen.[a]	If prolonged or severe, exclude infectious or noninfectious (e.g., lactose intolerance) causes of diarrhea. Reassure patient that this adverse effect generally improves over time (usually 6–8 weeks). Consider switching ARV regimen in persistent and severe cases. Although treatment data in children are lacking, potentially useful modalities include: • Dietary modification • Bulk-forming agents (psyllium) • Antimotility agents (loperamide) • Crofelemer is FDA-approved for treatment of ART-associated diarrhea only in adults ≥18 years of age; no pediatric data available.

Table 15c. Antiretroviral-Therapy-Associated Adverse Effects and Management Recommendations—Gastrointestinal Effects (Last updated May 22, 2018; last reviewed May 22, 2018) (page 2 of 2)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/Monitoring	Management
Pancreatitis	More Common: • ddI, d4T (especially if administered concurrently) Rare: • RTV-boosted PIs • Other ARVs	Onset: • Anytime, usually after months of therapy Presentation: • Emesis, abdominal pain, elevated amylase and lipase (asymptomatic hyperamylasemia or elevated lipase do not in and of themselves indicate pancreatitis)	<2% in recent series	Use of concomitant medications associated with pancreatitis (e.g., TMP-SMX, pentamidine, ribavirin) Hypertriglyceridemia Advanced disease Previous episode of pancreatitis Alcohol use	**Do not use** ddI or d4T (individually or together) as part of an ARV regimen.[a]	Discontinue offending agent—**avoid reintroduction**. Manage symptoms of acute episode. If associated with hypertriglyceridemia, consider interventions to lower TG levels.

[a] ddI, d4T, and NFV are **no longer recommended**; these ARVs should not be used (individually or together) as part of an ARV regimen. Co-administration of ddI and d4T is **contraindicated (no exceptions)**.

Key to Acronyms: 3TC = lamivudine; ART = antiretroviral therapy; ARV = antiretroviral; d4T = stavudine; ddI = didanosine; DRV/r = darunavir/ritonavir; FDA = Food and Drug Administration; FTC = emtricitabine; LPV/r = lopinavir/ritonavir; NFV = nelfinavir; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; RTV = ritonavir; TG = triglyceride; TMP-SMX = trimethoprim sulfamethoxazole; ZDV = zidovudine

Table 15d. Antiretroviral-Therapy-Associated Adverse Effects and Management Recommendations—Hematologic Effects (Last updated May 22, 2018; last reviewed May 22, 2018) (page 1 of 2)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/Monitoring	Management
Anemia[a]	ZDV	Onset: • Variable, weeks to months Presentation *Most Commonly:* • Asymptomatic or mild fatigue • Pallor • Tachypnea *Rarely:* • Congestive heart failure	Newborns Exposed to HIV: • Severe anemia is uncommon, but may be seen coincident with physiologic Hgb nadir. Children with HIV Taking ARVs: • 2–3 times more common with ZDV-containing regimens	Newborns Exposed to HIV: • Premature birth • *In utero* exposure to ZDV-containing regimens • Advanced maternal HIV • Neonatal blood loss • Combination ARV prophylaxis, particularly with ZDV plus 3TC Children with HIV Taking ARVs: • Underlying hemoglobinopathy (e.g., sickle cell disease, G6PD deficiency) • Myelosuppressive drugs (e.g., TMP-SMX, rifabutin) • Iron deficiency • Advanced or poorly controlled HIV disease • Malnutrition	Newborns Exposed to HIV: • Obtain CBC at birth. • Consider repeat CBC at 4 weeks for neonates who are at higher risk (e.g., those born prematurely or known to have low birth Hgb) and if ZDV is continued beyond 4 weeks. Children with HIV Taking ARVs: • Avoid ZDV in children with severe anemia when alternative agents are available. • Obtain CBC as part of routine care (see Clinical and Laboratory Monitoring)	Newborns Exposed to HIV: • Anemia rarely requires intervention unless Hgb is <7.0 g/dL or it is associated with symptoms. • ZDV administration can be limited to 4 weeks in low-risk neonates (see Antiretroviral Management of Newborns with Perinatal HIV Exposure or Perinatal HIV). Children with HIV Taking ARVs: • Discontinue non-ARV, marrow-toxic drugs, if feasible. • Treat coexisting iron deficiency, OIs, and malignancies. • For persistent severe anemia thought to be associated with ARVs (typically macrocytic anemia), switch to a regimen that does not contain ZDV.
Macrocytosis	ZDV	Onset: • Within days to weeks of starting therapy • MCV often >100 fL Presentation: • Asymptomatic • Sometimes associated with anemia	>90% to 95%, all ages	None	None required—detected if CBC obtained as part of routine care (see Clinical and Laboratory Monitoring section).	None required

Table 15d. Antiretroviral-Therapy-Associated Adverse Effects and Management Recommendations—Hematologic Effects (Last updated May 22, 2018; last reviewed May 22, 2018) (page 2 of 2)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/Monitoring	Management
Neutropenia[a]	ZDV	Onset: • Variable Presentation: • Asymptomatic	Newborns Exposed to HIV: • Rare Children with HIV Taking ARVs: • 2% to 4% of children on ARVs • Highest rates with ZDV-containing regimens	Newborns Exposed to HIV: • *In utero* exposure to ARVs • Combination ARV prophylaxis, particularly with ZDV plus 3TC Children with HIV Taking ARVs: • Advanced or poorly controlled HIV infection • Myelosuppressive drugs (e.g., TMP-SMX, ganciclovir, hydroxyurea, rifabutin)	Children with HIV Taking ARVs: • Obtain CBC as part of routine care.	Newborns Exposed to HIV: • No established threshold for intervention; some experts would consider using an alternative NRTI for prophylaxis if ANC reaches <500 cells/mm^3. ZDV administration can be limited to 4 weeks in low-risk neonates (see Antiretroviral Management of Newborns with Perinatal HIV Exposure or Perinatal HIV). Children with HIV Taking ARVs: • Discontinue non-ARV marrow-toxic drugs, if feasible. • Treat coexisting OIs and malignancies. • For persistent severe neutropenia thought to be associated with ARVs, change to a regimen that does not contain ZDV.

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

Key to Acronyms: 3TC = lamivudine; ANC = absolute neutrophil count; ARV = antiretroviral; CBC = complete blood count; dL = deciliter; fL = femtoliter; G6PD = glucose-6-phosphate dehydrogenase; Hgb = hemoglobin; MCV = mean cell volume; NRTI = nucleoside reverse transcriptase inhibitor; OI = opportunistic infection; TMP-SMX = trimethoprim-sulfamethoxazole; ZDV = zidovudine

Table 15e. Antiretroviral-Therapy-Associated Adverse Effects and Management Recommendations—Hepatic Events

(Last updated May 22, 2018; last reviewed May 22, 2018) (page 1 of 2)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/Monitoring	Management
Hepatitis	Most ARVs have been associated with hepatitis, but there is a strong association with NVP, EFV, and TPV. NVP, EFV, ABC, RAL, and MVC have been associated with hepatitis in context of HSRs. NRTIs have been associated with lactic acidosis and hepatic steatosis, especially ZDV, d4T, and ddI (co-administering d4T and ddI poses the highest risk). d4T or ddI **are no longer recommended** for use in an ARV regimen.	Onset: • An acute toxic hepatitis most commonly occurs within the first few months of therapy (but can occur later). • Steatosis presents after months to years of therapy. • Patients with HBV coinfection may develop flare of hepatitis with the initiation or withdrawal of 3TC, FTC, TDF, or TAF. Flare may also occur with the emergence of resistance to 3TC or FTC (especially if receiving only 1 anti-HBV agent). Note that HBV has a high genetic barrier for resistance to TDF and TAF. • Hepatitis may represent IRIS early in therapy, especially in patients with HBV- and HCV-coinfection. Presentation: • Asymptomatic elevation of AST and ALT • Symptomatic hepatitis with nausea, fatigue, and jaundice • Hepatitis may present in context of HSR with rash, lactic acidosis, and hepatic steatosis.	Uncommon	HBV or HCV coinfection Underlying liver disease Use of other hepatotoxic medications and supplements (e.g., St. John's wort [*Hypericum perforatum*], chaparral [*Larrea tridentate*], germander [*Teucrium chamaedrys*]) Alcohol use Pregnancy Obesity 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 • Population- specific HLA types[a] • Higher drug concentrations for PIs, particularly TPV	Prevention: • Avoid concomitant use of hepatotoxic medications. • Do not use d4T or ddI (individually or together); co-administration is **contraindicated (no exceptions)**. • In patients with elevated hepatic enzymes (>5 to 10 times ULN) or chronic liver disease, most clinicians would avoid NVP. Monitoring *For ARVs Other Than NVP:* • Obtain AST and ALT at baseline and thereafter at least every 3–4 months,[b] or more frequently in at-risk patients (e.g., those with HBV or HCV coinfection or elevated baseline AST and ALT). *For NVP:* • Obtain AST and ALT at baseline, at 2 and 4 weeks, and then every 3 months.	Evaluate for other infectious and non-infectious causes and monitor closely. Asymptomatic: • Potentially offending ARVs should be discontinued if ALT or AST is >5 times ULN. Symptomatic: • Discontinue all ARVs and other potentially hepatotoxic drugs. • If a patient experiences hepatitis attributed to NVP, it should be permanently discontinued. • Consider viral causes of hepatitis: HAV, HBV, HCV, EBV, and CMV.

Table 15e. Antiretroviral-Therapy-Associated Adverse Effects and Management Recommendations—Hepatic Events

(Last updated May 22, 2018; last reviewed May 22, 2018) (page 2 of 2)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/Monitoring	Management
Indirect Hyper-bilirubinemia	ATV (with either RTV or COBI), IDV	Onset: • First months of therapy Presentation: • May be asymptomatic or associated with jaundice • Direct bilirubin may be normal or slightly elevated when levels of indirect bilirubin are very high. • Normal AST and ALT	In long-term follow-up, 9% of children receiving ATV had at least 1 total bilirubin level >5 times ULN and 1.4% experienced jaundice.	N/A	Prevention: • IDV is not FDA-approved or recommended for use in the pediatric population. Monitoring: • No ongoing monitoring needed. After an initial rise over the first few months of therapy, unconjugated bilirubin levels generally stabilize; levels may improve over time.	Isolated indirect hyperbilirubinemia is not indication for cessation of a potentially offending ARV. Psychological impact of jaundice should be evaluated, and alternative agents considered.
Non-Cirrhotic Portal Hypertension	d4T, ddI d4T or ddI are **no longer recommended** for use in an ARV regimen.	Onset: • Generally after years of therapy Presentation: • GI bleeding, esophageal varices, hypersplenism • Mild elevations in AST and ALT, moderate increases in ALP, and pancytopenia (due to hypersplenism) Liver Biopsy *Variety of Findings, Most Commonly:* • Nodular regenerative hyperplasia • Hepatoportal sclerosis	Rare	Prolonged exposure to ARV therapy, especially ddI and the combination of d4T and ddI.	Prevention: • Do not use d4T, or ddI (individually or together); co-administration is **contraindicated (no exceptions)**. Monitoring: • No specific monitoring	Discontinue potentially offending agents. Manage complications of GI bleeding and esophageal varices.

[a] For example, HLA-DRB1*0101 in whites, HLA-DRB1*0102 in South Africans, and HLA-B35 in Thai and whites.

[b] Less frequent monitoring can be considered in children whose clinical status is stable for more than 2–3 years (see Clinical and Laboratory Monitoring of Pediatric HIV Infection).

Key to Acronyms: 3TC = lamivudine; ABC = abacavir; ALP = alkaline phosphatase; ALT = alanine transaminase; ARV = antiretroviral; AST = aspartate aminotransferase; ATV = atazanavir; CD4 = CD4 T lymphocyte; CMV = cytomegalovirus; COBI = cobicistat; d4T = stavudine; ddI = didanosine; EBV = Epstein-Barr virus; EFV = efavirenz; FDA = Food and Drug Administration; FTC = emtricitabine; GI = gastrointestinal; HAV = hepatitis A virus; HBV = hepatitis B virus; HCV = hepatitis C virus; HLA = human leukocyte antigen; HSR = hypersensitivity reaction; IDV = indinavir; IRIS = immune reconstitution inflammatory syndrome; MVC = maraviroc; NRTI = nucleoside reverse transcriptase inhibitor; NVP = nevirapine; PI = protease inhibitor; RAL = raltegravir; RTV = ritonavir; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; TPV = tipranavir; ULN = upper limit of normal; ZDV = zidovudine

Table 15f. Antiretroviral-Therapy-Associated Adverse Effects and Management Recommendations—Insulin Resistance, Asymptomatic Hyperglycemia, Diabetes Mellitus (Last updated May 22, 2018; last reviewed May 22, 2018)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/Monitoring	Management
Insulin Resistance, Asymptomatic Hyperglycemia, DM[a]	NRTIs: • ZDV • d4T • ddI d4T or ddI **are no longer recommended** for use in an ARV regimen. PIs: • LPV/r • Rarely other PIs	Onset: • Weeks to months after beginning therapy Presentation: • Asymptomatic fasting hyperglycemia (possibly in the setting of lipodystrophy), metabolic syndrome, or growth delay • Symptomatic DM (rare)	Children: • Insulin resistance, 6% to 12% • Impaired fasting glucose, 0% to 7% • Impaired glucose tolerance, 3% to 4% • DM, 0.2 per 100-child-years	Risk Factors for Type 2 DM: • Lipodystrophy • Metabolic syndrome • Family history of DM • High BMI (obesity)	Prevention: • Lifestyle modification • Do not use d4T or ddI (individually or together); co-administration is **contraindicated (no exceptions)**. • Avoid ZDV when possible. Monitoring: • Monitor for signs of DM, change in body habitus, and acanthosis nigricans. *Obtain RPG Levels at:* • Initiation of ARV therapy • 3–6 months after therapy initiation • 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 (e.g., a diet low in saturated fat, cholesterol, trans fat, and refined sugars; increased physical activity; cessation of smoking); recommend consultation with dietician. Change NRTI backbone (e.g., from ZDV, d4T, or ddI to TAF, TDF, or ABC). 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 75 g-OGTT (or if <43 kg, 1.75 g/kg of glucose up to a maximum of 75 g); 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 RPG and FPG levels.

Key to Acronyms: ABC = abacavir; ARV = antiretroviral; BMI = body mass index; d4T = stavudine; ddI = didanosine; dL = deciliter; DM = diabetes mellitus; FPG = fasting plasma glucose; HgbA1c = glycosylated hemoglobin; LPV/r = lopinavir/ritonavir; NRTI = nucleoside reverse transcriptase inhibitor; OGTT = oral glucose tolerance test; PG = plasma glucose; PI = protease inhibitor; RPG = random plasma glucose; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; ZDV = zidovudine

Table 15g. Antiretroviral-Therapy-Associated Adverse Effects and Management Recommendations—Lactic Acidosis

(Last updated May 22, 2018; last reviewed May 22, 2018) (page 1 of 2)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/Monitoring	Management
Lactic Acidosis	NRTIs: • d4T and ddI have the highest risk when co-administered, followed by ZDV. • d4T or ddI **are not recommended** in an ARV regimen. • 3TC, FTC, ABC, TAF, and TDF are less likely to induce mitochondrial dysfunction of clinical significance.	Onset: • 1–20 months after starting therapy (median onset was 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 **Note:** Patients may present with acute multi-organ failure (e.g., fulminant hepatic, pancreatic, respiratory failure).	The following information is based on studies that included d4T and ddI. Chronic, Asymptomatic Mild Hyperlactatemia (2.1–5.0 mmol/L) *Adults:* • 15% to 35% of adults receiving NRTI therapy for >6 months *Children:* • 29% to 32% Symptomatic Severe Hyperlactatemia (>5.0 mmol/L) *Adults:* • 0.2% to 5.7% Symptomatic Lactic Acidosis/Hepatic Steatosis: • Rare in all age groups (1.3–11 episodes per 1,000 person-years; increased incidence with the use of d4T/ddI when co-administered), but associated with a high fatality rate (33% to 58%)	Adults: • Female sex • High BMI • Chronic HCV infection • African-American race • Prolonged NRTI use (particularly d4T and ddI) • Co-administration of ddI with other agents (e.g., d4T, TDF, RBV, tetracycline) • Co-administration of TDF with metformin • Overdose of propylene glycol • CD4 count <350 cells/mm^3 • Acquired riboflavin or thiamine deficiency • Possibly pregnancy Preterm Infants or Any Neonates before Post-Menstrual Age of 42 Weeks and a Postnatal Age of ≥14 Days has Been Attained: • Exposure to propylene glycol (e.g., present as a diluent in LPV/r oral solution). A diminished ability to metabolize propylene glycol may lead to accumulation and potential adverse events.	Prevention: • Do not use d4T or ddI (individually or together) in an ARV regimen; co-administration is **contraindicated (no exceptions)**. • Due to the presence of propylene glycol as a diluent, LPV/r oral solution should not be used in preterm neonates or any neonate before a postmenstrual age of 42 weeks and a postnatal age of ≥14 days has been attained. • 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): • Replace ddI and d4T with other ARVs. • As an 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 1 Test): • Discontinue all ARVs. • Provide supportive therapy (IV 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 Q10, vitamin C) Following resolution of clinical and laboratory abnormalities, resume therapy, either with a NRTI-sparing regimen or a revised NRTI-containing regimen instituted with caution, using NRTIs less likely to induce mitochondrial dysfunction (ABC, TAF, or TDF preferred; possibly FTC or 3TC), and lactate should be monitored monthly 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.

Table 15g. Antiretroviral-Therapy-Associated Adverse Effects and Management Recommendations—Lactic Acidosis

(Last updated May 22, 2018; last reviewed May 22, 2018) (page 2 of 2)

Key to Acronyms: 3TC = lamivudine; ABC = abacavir; ARV = antiretroviral; BMI = body mass index; CD4 = CD4 T lymphocyte; d4T = stavudine; ddI = didanosine; FTC = emtricitabine; HCV = hepatitis C virus; IV = intravenous; LPV/r = lopinavir/ritonavir; NRTI = nucleoside reverse transcriptase inhibitor; RBV = ribavirin; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; THAM = tris (hydroxymethyl) aminomethane; ZDV = zidovudine

Table 15h. Antiretroviral-Therapy-Associated Adverse Effects and Management Recommendations—Lipodystrophy, Lipohypertrophy, Lipoatrophy (Last updated May 22, 2018; last reviewed May 22, 2018) (page 1 of 2)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/Monitoring	Management
Lipodystrophy (Fat Maldistribution) General Information	See below for specific associations.	Onset: • Trunk and limb fat initially increase; peripheral fat wasting may not appear for 12–24 months after ART initiation.	Varies greatly depending upon measure and comparator group. Frequency may be up to 15% with current regimens.	Genetic predisposition Puberty HIV-associated inflammation Older age Longer duration of ART Body habitus	See below.	See below. Physicians should perform a regimen review and consider changing the regimen when lipodystrophy occurs. Improvement following regimen change is variable. Improvement may occur after several months or years, or it may not occur at all.
Central Lipohypertrophy or **Lipo-accumulation**	Can occur in the absence of ART, but most often associated with PIs and EFV.	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, particularly with EFV.	Up to 15% with current regimens	Obesity before initiation of therapy Sedentary lifestyle	Prevention: • Calorically appropriate low-fat diet and exercise Monitoring: • BMI measurement • Body circumference and waist-hip ratio	Counsel patient on lifestyle modification and dietary interventions (e.g., maintaining a calorically appropriate healthy diet that is low in saturated fats and simple carbohydrates, and starting an exercise regimen, especially strength training). Recommend smoking cessation (if applicable) to decrease future CVD risk. Consider switching patient from PIs and EFV to an INSTI. 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 • Recombinant human leptin • Anabolic steroids • Liposuction

Table 15h. Antiretroviral-Therapy-Associated Adverse Effects and Management Recommendations—Lipodystrophy, Lipohypertrophy, Lipoatrophy (Last updated May 22, 2018; last reviewed May 22, 2018) (page 2 of 2)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/Monitoring	Management
Facial/ Peripheral Lipoatrophy	Most associated with thymidine analogue NRTIs (d4T > ZDV)	Presentation: • Thinning of subcutaneous fat in face, buttocks, and extremities, measured as a decrease in trunk/limb fat by DXA or triceps skinfold thickness. Preservation of lean body mass distinguishes lipoatrophy from HIV-associated wasting.	• Up to 15% with currently used regimens	Underweight before ART	Prevention: • Do not use ddI or d4T (individually or together); they **are no longer recommended** as part of an ARV regimen. **Co-administration of ddI and d4T is contraindicated (no exceptions)**. Monitoring: • Patient self-report and physical exam are the most sensitive methods of monitoring lipoatrophy.	Replace ZDV with other NRTIs if possible. d4T should never be used. 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 • Thiazolidinediones

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

Table 15i. Antiretroviral-Therapy-Associated Adverse Effects and Management Recommendations—Nephrotoxic Effects

(Last updated May 22, 2018; last reviewed May 22, 2018) (page 1 of 2)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/Monitoring	Management
Urolithiasis/ Nephrolithiasis	ATV, IDV DRV causes crystalluria, but it is not associated with nephrolithiasis.	Onset: • Weeks to months after starting therapy Clinical Findings: • Crystalluria • Hematuria • Pyuria • Flank pain • Sometimes increased creatinine	ATV-related nephrolithiasis occurs in <10% of patients. IDV-related nephrolithiasis occurs more often in children (29%) than adults (12.4%).	In adults, elevated urine pH (>5.7) Unknown in children	Prevention: • Maintain adequate hydration. • IDV is not FDA-approved for use in children and should be avoided. Monitoring: • Obtain urinalysis at least every 6–12 months.	Provide adequate hydration and pain control; consider using alternative ARV. If patient is on IDV, discontinue.
Renal Dysfunction	TDF	Onset: • Variable; in adults, weeks to months after initiation of therapy • Hypophosphatemia appears at a median of 18 months. • Glucosuria may occur after a year of therapy. • Abnormal urine protein/ osmolality ratio may be an early indicator. Presentation *More Common:* • Increased serum creatinine, proteinuria, normoglycemic glucosuria. Hypophosphatemia, usually asymptomatic; may present with bone and muscle pain, weakness *Less Common:* • Renal failure, acute tubular necrosis, Fanconi syndrome, proximal renal tubulopathy, interstitial nephritis, nephrogenic diabetes insipidus with polyuria	Adults: • Approximately 2% with increased serum creatinine • Approximately 0.5% with severe renal complications Children: • Approximately 4% with hypophosphatemia or proximal tubulopathy; frequency increases with prolonged TDF therapy, advanced HIV infection, or concomitant use of ddI.	Risk May Increase in Children with the Following Characteristics: • Aged >6 years • Black race, Hispanic/ Latino ethnicity • Advanced HIV infection • Hypertension • Diabetes • Concurrent use of ddI or PIs (especially LPV/r), and preexisting renal dysfunction • Risk increases with longer duration of TDF treatment.	Monitor urine protein, glucose or urinalysis, and serum creatinine at 3- to 6-month intervals. For patients taking TDF, some panelists add serum phosphate to the list of routine labs to monitor. Measure serum phosphate if the patient experiences persistent proteinuria or glucosuria, or has symptoms of bone pain, muscle pain, or weakness. Because toxicity risk increases with duration of TDF treatment, do not decrease the frequency of monitoring over time.	If TDF is the likely cause, consider using alternative ARV. TAF has significantly less toxicity than TDF. ddI **is no longer recommended and should be discontinued**.

Table 15i. Antiretroviral-Therapy-Associated Adverse Effects and Management Recommendations—Nephrotoxic Effects

(Last updated May 22, 2018; last reviewed May 22, 2018) (page 2 of 2)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/Monitoring	Management
Elevation in Serum Creatinine	DTG, COBI, RPV	Onset: • Within a month of starting treatment Presentation: • Asymptomatic. These drugs decrease renal tubular secretion of creatinine, leading to an increase in measured serum creatinine without a true change in eGFR.	Common Need to distinguish between true change in eGFR and other causes. True change might be associated with other medical conditions, continuing rise of serum creatinine with time, and albuminuria.	N/A	Monitor serum creatinine. Assess for renal dysfunction if serum creatinine increases by >0.4 mg/dL or if increases continue over time.	No need to change therapy. Reassure patient about the benign nature of the laboratory abnormality.

Key to Acronyms: ARV = antiretroviral; ATV = atazanavir; COBI = cobicistat; ddI = didanosine; DRV = darunavir; DTG = dolutegravir; eGFR = estimated glomerular filtration rate; FDA = Food and Drug Administration; IDV = indinavir; LPV/r = lopinavir/ritonavir; PI = protease inhibitor; RPV = rilpivirine; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate

Table 15j. Antiretroviral-Therapy-Associated Adverse Effects and Management Recommendations—Osteopenia and Osteoporosis (Last updated May 22, 2018; last reviewed May 22, 2018)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/Monitoring	Management
Osteopenia and Osteoporosis	Any ART regimen Specific Agents of Concern: • TDF • PIs, especially LPV/r	Onset: • Any age; decrease in BMD usually seen soon after initiation of ART. Presentation: • Usually asymptomatic • Rarely presents as osteoporosis, a clinical diagnosis defined by evidence of bone fragility (e.g., fracture with minimal trauma).	BMD *z* Score Less Than -2.0: • <10% in U.S. cohorts • Approximately 20% to 30% in international cohorts	Longer duration and greater severity of HIV disease Vitamin D insufficiency/ deficiency Delayed growth or pubertal delay Low BMI Lipodystrophy Non-black race Smoking Prolonged systemic corticosteroid use Medroxyprogesterone use Lack of weight-bearing exercise	Prevention: • Ensure sufficient calcium intake and vitamin D sufficiency. • Encourage weight-bearing exercise. • Minimize modifiable risk factors (e.g., smoking, low BMI, use of steroids or medroxyprogesterone). • Use TAF instead of TDF whenever possible. Monitoring: • Assess nutritional intake (calcium, vitamin D, and total calories). • Strongly consider measuring serum 25-OH-vitamin D levels, particulary in those patients taking ARVs of concern.[a] • Obtain a DXA.[b]	Same options as for prevention. Consider changing the ARV regimen (e.g., switching from TDF to TAF, and/or from LPV/r to EFV or an INSTI whenever possible). Treat with vitamin D3 to raise serum 25-OH-vitamin D concentrations to >30 ng/mL. The role of bisphosphonates in managing osteopenia and osteoporosis in children with HIV has not been established.

[a] Some experts periodically measure 25-OH-vitamin D. This is especially important in youth with HIV infection who live in urban areas; the prevalence of vitamin D insufficiency is high in that population.

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

Key to Acronyms: ART = antiretroviral therapy; ARV = antiretroviral; BMD = bone mineral density; BMI = body mass index; DXA = dual-energy x-ray absorptiometry; EFV = efavirenz; INSTI = integrase strand transfer inhibitor; LPV/r = lopinavir/ritonavir; PI = protease inhibitor; TAF= tenofovir alafenamide; TDF = tenofovir disoproxil fumarate

Table 15k. Antiretroviral-Therapy-Associated Adverse Effects and Management Recommendations—Peripheral Nervous System Toxicity (Last updated May 22, 2018; last reviewed May 22, 2018)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency[a]	Risk Factors	Prevention/ Monitoring	Management
ARV Toxic Neuropathy[b]	d4T, ddI d4T or ddI are **no longer recommended** for use in an ARV regimen. PIs rarely, primarily IDV	Onset: • Weeks to months Presentation: • Decreased sensation • Aching, burning, painful numbness • Hyperalgesia • Allodynia • Decreased or absent ankle reflexes *Distribution:* • Bilateral soles of feet, ascending to legs and fingertips	Children: • Around 1% overall • 10% to 25% in children taking d4T Adults: • Up to 50% in adults taking d4T	• Pre-existing neuropathy • Elevated triglyceride levels • Poor nutrition • More advanced HIV disease • Concomitant use of other neurotoxic agents (e.g., INH) • Some mitochondrial DNA haplogroups may have increased risk.	Do not use d4T, ddI, or IDV. Co-administration of ddI and d4T **is contraindicated (no exceptions)**. Monitor for symptoms and signs of peripheral neuropathy.	Investigate potential causes, including non-ARV medications and nutritional deficiencies. Discontinue offending agent. Topical capsaicin 8% may be helpful. Consider referral to a neurologist. Data are insufficient to allow the Panel to recommend use of any of the following modalities: tricyclic antidepressants, gabapentin, gregabalin, mexiletine, lamotrigine, and acupuncture or other complementary approaches.

[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; IDV = indinavir; INH = isoniazid; PI = protease inhibitor; the Panel = The Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV

Table 15I. Antiretroviral-Therapy-Associated Adverse Effects and Management Recommendations—Rash and Hypersensitivity Reactions (Last updated May 22, 2018; last reviewed May 22, 2018) (page 1 of 5)

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 new ARV(s) Presentation: • Most rashes are mild-to-moderate, diffuse maculopapular eruptions **Note:** A rash can be the initial manifestation of systemic hypersensitivity (see SJS/TEN/EM Major and HSR sections below).	Common (>10% Adults and/or Children): • NVP • EFV • ETR • FPV • FTC Less Common (5% to 10%): • ABC • DRV • TPV • TDF Unusual (2% to 4%): • LPV/r • RAL • MVC • RPV	• Sulfonamide allergy is a risk factor for rash with PIs containing a sulfonamide moiety (FPV, DRV, and TPV) • Polymorphisms in CYP2B6 and multiple HLA loci may confer increased risk of rash with NVP	When Starting NVP or Restarting After Interruptions >14 Days: • Utilize once-daily lead-in dosing (see NVP section).[a] • Avoid the use of systemic corticosteroids during NVP dose escalation. • Assess patient for rash severity, mucosal involvement, and other signs of systemic reaction.	Mild-to-Moderate Maculopapular Rash Without Systemic or Mucosal Involvement: • Most rashes will resolve without intervention; ARVs can be continued while monitoring.[a] • Antihistamines may provide some relief. Severe Rash (e.g., Blisters, Bullae, Ulcers, Skin Necrosis) and/or Rash Accompanied by Systemic Symptoms (e.g., Fever, Arthralgia, Edema) and/or Rash Accompanied by Mucous Membrane Involvement (e.g., conjunctivitis): • Manage as SJS/TEN/EM major (see below) Rash in Patients Receiving NVP: • Given elevated risk of HSR, measure hepatic transaminases. • If hepatic transaminases are elevated, NVP should be discontinued and not restarted (see HSR-NVP below).
	T-20	Onset: • First few days to weeks after starting new ARV(s) Presentation: • Local injection site reactions with pain, erythema, induration, nodules and cysts, pruritus, and ecchymosis • Often multiple reactions at the same time	Children and Adults: • >90%	Unknown	• Routinely assess patient for local reactions. • Rotate injection sites. • Massage area after injection.	• Continue the agent as tolerated by the patient. • Ensure patient is injecting as per instructions. • Rotate injection sites.

Table 15l. Antiretroviral-Therapy-Associated Adverse Effects and Management Recommendations—Rash and Hypersensitivity Reactions (Last updated May 22, 2018; last reviewed May 22, 2018) (page 2 of 5)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/Monitoring	Management
SJS/TEN/EM Major	Many ARVs, especially NNRTIs (see Estimated Frequency column)	Onset: • First few days to weeks after starting new ARV(s) Presentation: • Initial rash may be mild, but often becomes painful, evolving to blister/bulla formation with necrosis in severe cases. Usually involves mucous membrane ulceration and/or conjunctivitis. Systemic symptoms may also 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: • Utilize once-daily lead-in dosing (see NVP section).[a] • Counsel families to report symptoms as soon as they appear.	• Discontinue all ARVs and other possible causative agents (e.g., TMP-SMX). • 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/TEN/EM major occurring with 1 NNRTI, many experts would avoid use of other NNRTIs.
DRESS	EFV, ETR, NVP, RAL, RPV, DRV	Onset: • 1–8 weeks after starting new ARV(s) Presentation: • Fever • Lymphadenopathy • Facial swelling • Morbilliform to polymorphous rash • Peripheral eosinophilia • Atypical circulating lymphocytes • Internal organ involvement (particularly liver and/or renal)	Rare	Unknown	• Obtain CBC, AST, ALT, and creatinine from a patient presenting with suggestive symptoms.	• Discontinue all ARVs and other possible causative agents (e.g., TMP-SMX). • Role for steroids unclear; suggest consultation with specialist. • Provide supportive care for end-organ disease. • Do not reintroduce the offending medication.

Table 15l. Antiretroviral-Therapy-Associated Adverse Effects and Management Recommendations—Rash and Hypersensitivity Reactions (Last updated May 22, 2018; last reviewed May 22, 2018) (page 3 of 5)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/Monitoring	Management
HSR With or without skin involvement and excluding SJS/TEN	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, and respiratory symptoms (e.g., dyspnea). • Symptoms worsen to include hypotension and vascular collapse with continuation of ABC. With rechallenge, symptoms can mimic anaphylaxis.	2.3% to 9% (varies by ethnicity).	• HLA-B*5701 (HSR very uncommon in people who are HLA-B*5701-negative); combination of HLA-DR7 plus HLA-DQ3 also confers risk. • HSR risk is higher in those of white race compared to those of black or East Asian race.	• Screen for HLA-B*5701. **ABC should not be prescribed if HLA-B*5701 is present.** The medical record should clearly indicate that ABC is **contraindicated**. • When starting ABC, 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 (e.g., a concurrent 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 15l. Antiretroviral-Therapy-Associated Adverse Effects and Management Recommendations—Rash and Hypersensitivity Reactions (Last updated May 22, 2018; last reviewed May 22, 2018) (page 4 of 5)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/Monitoring	Management
HSR With or without skin involvement and excluding SJS/TEN	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, and jaundice) with or without skin rash that may progress to hepatic failure with encephalopathy	4% (2.5% to 11%)	Adults: • Treatment-naive with higher CD4 count (>250 cells/mm^3 in women; >400 cells/mm^3 in men). • Female sex (risk is 3-fold higher in females compared with males). Children: • NVP hepatotoxicity and HSR are less common in pre-pubertal children than in adults and uncommon in infants. • High CD4 percentage is associated with increased risk of NVP toxicity. In the PREDICT study, the risk of NVP toxicity (rash, hepatotoxicity, hypersensitivity) was 2.65 times greater in children who had CD4 percentages ≥15% than in children who had CD4 percentages <15%.	When Starting NVP or Restarting After Interruptions >14 Days: • A 2-week lead-in period with once-daily dosing, followed by dose escalation to twice daily as recommended, may reduce the risk of reaction.[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 as post-exposure prophylaxis outside of the neonatal period.	• Discontinue ARVs. • Consider other causes for hepatitis and discontinue all hepatotoxic medications. • Provide supportive care as indicated and monitor the patient closely. • Do not re-introduce 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.
	T-20, 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 with T-20 or ETR is not recommended.

Table 15l. Antiretroviral-Therapy-Associated Adverse Effects and Management Recommendations—Rash and Hypersensitivity Reactions (Last updated May 22, 2018; last reviewed May 22, 2018) (page 5 of 5)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/Monitoring	Management
HSR With or without skin involvement and excluding SJS/TEN	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.
	DTG	Rash with hepatic dysfunction	Rare	Unknown	• Obtain AST and ALT in patients with rash or other symptoms of hypersensitivity.	• Discontinue all ARVs. • Rechallenge with DTG is contraindicated

[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 sub-therapeutic drug levels. Management of children who have persistent mild or moderate rash after the lead-in period should be individualized and an expert in HIV care should be consulted. **NVP should be stopped and not restarted** if the rash is severe or is worsening or progressing.

Key to Acronyms: ABC = abacavir; ALT = alanine transaminase; ARV = antiretroviral; AST = aspartate aminotransferase; ATV = atazanavir; CBC = complete blood count; CD4 = CD4 T lymphocyte; CYP = cytochrome P; ddI = didanosine; DRESS = drug rash with eosinophilia and systemic symptoms; DRV = darunavir; DTG = dolutegravir; EFV = efavirenz; EM = erythema multiforme; ETR = etravirine; FPV = fosamprenavir; FTC = emtricitabine; HLA = human leukocyte antigen; 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; PEP = post-exposure prophylaxis; PI = protease inhibitor; RAL = raltegravir; RPV = rilpivirine; SJS = Stevens-Johnson syndrome; T-20 = enfuvirtide TDF = tenofovir disoproxil fumarate; TEN = toxic epidermal necrolysis; TPV = tipranavir; ZDV = zidovudine

Table 16. Examples of Changes in Antiretroviral Regimen Components that Are Made for Reasons of Simplification, Convenience, and Safety Profile in Children Who Have Sustained Virologic Suppression on Their Current Regimen (page 1 of 2)

Note: This list is not exhaustive and does not necessarily contain all potential treatment options. Instead, it shows examples of what kinds of changes can be made. The comments provided in the table are relevant only to the potential ARV change are listed and do not include all relevant information. Please refer to the individual drug sections in Appendix A: Pediatric Antiretroviral Drug Information for further information.

Current ARV Drug(s)	Age, Weight, and SMR Requirements	Potential ARV Switch	Comment
NRTIs			
ABC or 3TC Twice Daily	Aged ≥1 year	ABC once daily	See Abacavir[a] and Lamivudine sections in Appendix A: Pediatric Antiretroviral Drug Information for full discussion of once-daily dosing.
	Aged ≥3 years	3TC once daily	
ZDV, ddI, or d4T[b]	Aged ≥3 months	ABC	Less long-term mitochondrial toxicity. Children aged ≥1 year can take ABC once daily (see Abacavir[a] in Appendix A: Pediatric Antiretroviral Drug Information).
	Aged ≥2 years	TDF	TDF is a reasonable, once-daily option for HLA-B*5701–positive children who are unable to take ABC. TDF is available in low-strength combination tablets with FTC for use in children weighing ≥17 kg. TAF is preferred for children weighing ≥25 kg.
	Weighing ≥25 kg	TAF[c]	Less long-term mitochondrial toxicity. Once-daily dosing. Co-formulation with other ARV drugs can further reduce pill burden. TAF preferred over TDF for lower bone and renal toxicity. See TAF in Appendix A: Pediatric Antiretroviral Drug Information for full discussion.
NNRTIs			
EFV	N/A	RAL[d]	None
	Aged ≥3 months Weighing ≥5 kg	ATV/r	None
	Aged ≥3 years Weighing ≥10 kg	DRV/r	DRV/r may be administered once daily in children aged ≥12 years who do not have DRV resistance mutations.
	Weighing ≥25 kg	EVG as Genvoya	EVG is available as a component of the FDC EVG/COBI/FTC/TAF (Genvoya). Genvoya is a complete ARV regimen.
	Weighing ≥30 kg	DTG	Smaller pill, higher barrier to resistance given concern for adherence challenges developing in adolescents.
	Aged ≥ 12 years Weighing ≥35 kg	RPV	None
PIs			
LPV/r **Twice Daily**	N/A	RAL[d]	None
	Aged ≥3 years Weighing ≥10 kg	EFV	Once-daily dosing. Better palatability. Lower incidence of adverse lipid effects. See Efavirenz in Appendix A: Pediatric Antiretroviral Drug Information regarding concerns about dosing for children aged <3 years.
	Aged ≥3 months Weighing ≥5 kg	ATV/r	Once-daily dosing.
	Aged ≥3 years Weighing ≥10 kg	DRV/r	DRV/r is administered twice daily to patients aged <12 years, but may be administered once daily only in children aged ≥12 years who do not have DRV resistance mutations.
	Weighing ≥25 kg	EVG as Genvoya	EVG is available as a component of the FDC EVG/COBI/FTC/TAF (Genvoya). Genvoya is a complete ARV regimen.

Table 16. Examples of Changes in Antiretroviral Regimen Components that Are Made for Reasons of Simplification, Convenience, and Safety Profile in Children Who Have Sustained Virologic Suppression on Their Current Regimen (page 2 of 2)

Current ARV Drug(s)	Age, Weight, and SMR Requirements	Potential ARV Switch	Comment
LPV/r **Twice Daily**, continued	Weighing ≥30 kg	DTG	None
	Aged ≥12 years Weighing ≥35 kg	RPV	None
		BIC as Biktarvy	Once-daily dosing. BIC is available as a component of the FDC BIC/FTC/TAF (Biktarvy). Biktarvy is a complete ARV regimen; pediatric use is investigational.
Other			
Any Multi-Pill and/or Twice-Daily Regimen	Weighing ≥25 kg	EVG/COBI/FTC/TAF (Genvoya)	Once-daily dosing. Single pill. Alignment with adult regimens.
	Weighing ≥30 kg	FTC/TAF[c] (Descovy) plus DTG	Once-daily dosing. May be more desirable because of small pill sizes, even though it increases pill burden to 2 pills instead of 1.
	Weighing ≥35 kg SMR 4 or 5	EVG/COBI/FTC/TDF (Stribild)	Once-daily dosing. Single pill. Alignment with adult regimens.
	Aged ≥12 years Weighing ≥35 kg	FTC/RPV/TAF (Odefsey)	Once-daily dosing. Single pill. Alignment with adult regimens.
	Aged ≥12 years Weighing ≥35 kg	BIC/FTC/TAF[e] (Biktarvy)	Once-daily dosing. Single pill. Pediatric use is investigational.
	Aged ≥12 years Weighing ≥35 kg SMR 4 or 5	FTC/RPV/TDF (Complera)	Once-daily dosing. Single pill. Alignment with adult regimens.
	Weighing ≥40 kg	ABC/DTG/3TC (Triumeq)	Once-daily dosing. Single pill. Alignment with adult regimens. Large pill size may be a deterrent.
	Weighing ≥40 kg SMR 4 or 5	EFV/FTC/TDF (Atripla)	Once-daily dosing. Single pill. Alignment with adult regimens.

[a] For infants and young children being treated with liquid formulations of ABC, initiation with once-daily ABC is not generally recommended. In clinically stable patients with undetectable viral loads who have had stable CD4 T lymphocyte cell counts for more than 6 months (24 weeks) on twice-daily ABC, the dose can be changed from twice daily to once daily.

[b] d4T and ddI should be replaced with a safer drug **as soon as possible** because of concerns about long-term adverse events (see Stavudine and Didanosine in Appendix A: Pediatric Antiretroviral Drug Information).

[c] For children and adolescents weighing 25 kg to <35 kg, TAF can be used in combination with an INSTI or an NNRTI, but not a boosted PI. For children and adolescents weighing ≥35 kg, TAF can be used in combination with an INSTI, NNRTI, or a boosted PI.

[d] RAL HD once daily is only recommended for virologically suppressed children weighing ≥50 kg.

[e] Biktarvy has not been FDA-approved for use in patients aged <18 years but is being studied in children and adolescents aged ≥12 years to 18 years and weighing ≥35 kg.

Key to Acronyms: 3TC = lamivudine; ABC = abacavir; ARV = antiretroviral; ATV/r = atazanavir/ritonavir; BIC = bictegravir, COBI = cobicistat; d4T = stavudine; ddI = didanosine; DRV/r = darunavir/ritonavir; DTG = dolutegravir; EFV = efavirenz; EVG = elvitegravir; FDA = Food and Drug Administration; FDC = fixed-dose combination; FTC = emtricitabine; INSTI = integrase strand transfer inhibitor; LPV/r = lopinavir/ritonavir; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; RAL = raltegravir; RPV = rilpivirine; SMR = sexual maturity rating (previously Tanner stages); TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; TFV= tenofovir; ZDV = zidovudine

Table 17. Discordance Among Virologic, Immunologic, and Clinical Responses

Differential Diagnosis of Poor Immunologic Response Despite Virologic Suppression
Poor Immunologic Response Despite Virologic Suppression and Good Clinical Response: • Lab error (in CD4 or viral load result) • Misinterpretation of normal, age-related CD4 decline (i.e., the immunologic response is not actually poor) • Low pretreatment CD4 cell count or percentage • Adverse effects of using ZDV or the combination of TDF and ddI • Use of systemic corticosteroids or chemotherapeutic agents • Conditions that can cause low CD4 values, such as HCV, acute viral infections, TB, malnutrition, Sjogren's syndrome, sarcoidosis, and syphilis
Poor Immunologic and Clinical Responses Despite Virologic Suppression: • Lab error • Falsely low viral load result for an HIV strain/type that is not detected by viral load assay (HIV-1 non-M groups, non-B subtypes; HIV-2) • Persistent immunodeficiency soon after initiation of ART but before ART-related reconstitution • Primary protein-calorie malnutrition • Untreated TB • Malignancy
Differential Diagnosis of Poor Clinical Response Despite Adequate Virologic and Immunologic Responses
• IRIS • Previously unrecognized, pre-existing infection or condition (e.g., TB, malignancy) • Malnutrition • Clinical manifestations of previous organ damage: brain (e.g., strokes, vasculopathy), lungs (e.g., bronchiectasis) • New clinical event due to non-HIV illness or condition • New, otherwise unexplained HIV-related clinical event (treatment failure)

Key to Acronyms: ART = antiretroviral therapy; CD4 = CD4 T lymphocyte; ddI = didanosine; HCV = hepatitis C virus; IRIS = immune reconstitution inflammatory syndrome; TB = tuberculosis; TDF = tenofovir disoproxil fumarate; ZDV = zidovudine

Table 18. 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	New Regimen Options[a]
2 NRTIs plus NNRTI	• 2 NRTIs plus PI • 2 NRTIs plus INSTI
2 NRTIs plus PI	• 2 NRTIs plus INSTI • 2 NRTIs plus a different RTV-boosted PI • INSTI plus different RTV-boosted PI plus or minus an NNRTI and plus or minus NRTI(s)
2 NRTIs plus INSTI	• 2 NRTIs plus RTV-boosted PI • DTG (if not used in the prior regimen) plus RTV-boosted PI plus or minus 1 or 2 NRTIs
Failed Regimen(s) That Included NRTI(s), NNRTI(s), and PI(s)	• INSTI plus 2 NRTIs (if NRTIs are fully active) • INSTI plus 2 NRTIs plus or minus RTV-boosted PI (if NRTIs are not fully active) • INSTI plus or minus RTV-boosted PI plus or minus (ETR or RPV) plus or minus NRTI(s) (if minimal NRTI activity). Consider adding T-20 and/or MVC if additional active drug[s] needed.

[a] ART 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 and potent virologic suppression. **Please see individual drug profiles for information about age limitations (e.g., do not use DRV in children aged <3 years), drug interactions, and dose adjustments when devising a regimen for children with multiclass drug resistance.** Collaboration with a pediatric HIV specialist is especially important when choosing regimens for children with multiclass drug resistance. Regimens in this table are provided as examples, but the list is not exhaustive.

Key to Acronyms: DTG = dolutegravir; ETR = etravirine; INSTI = integrase strand transfer inhibitor; MVC = maraviroc; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; RPV = rilpivirine; RTV = ritonavir; T-20 = enfuvirtide