



Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

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Table 1. Outline of the Guidelines Development Process (page 1 of 2)

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 32 voting members who have expertise in management of HIV infection in infants, children, and adolescents. Members include representatives from the Committee on Pediatric AIDS of the American Academy of Pediatrics and community representatives with knowledge of pediatric HIV infection. The Panel also includes at least one representative from each of the following 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, <i>ex officio</i> member of the Panel. The US government representatives are appointed by their respective agencies; nongovernmental members are selected after an open announcement to call for nominations. Each member serves on the Panel for a 3-year term with an option for reappointment. A list of current members can be found in the Panel Roster .
Financial Disclosure	All members of the Panel submit a financial disclosure statement in writing annually, reporting any association with manufacturers of ARV drugs or diagnostics used for management of HIV infections. A list of the latest disclosures is available on the <i>AIDSinfo</i> 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. On some occasions, particularly when new information may affect patient safety, unpublished data presented at major conferences or prepared by the FDA and/or manufacturers as warnings to the public may be used as evidence to revise the guidelines.
Recommendation Grading	Described in Table 2 .
Method of Synthesizing Data	Each section of the guidelines is assigned to a small group of Panel members with expertise in the area of interest. The members synthesize the available data and propose recommendations to the Panel. The Panel discusses 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 for 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 and 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 <i>AIDSinfo</i> 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 <i>AIDSinfo</i> 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 yearly.
Public Comments	A 2-week public comment period follows release of the updated guidelines on the <i>AIDSinfo</i> 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
<p>A: Strong recommendation for the statement</p> <p>B: Moderate recommendation for the statement</p> <p>C: Optional recommendation for the statement</p>	<p>I: One or more randomized trials <u>in children</u>^a with clinical outcomes and/or validated laboratory endpoints</p> <p>I*: One or more randomized trials <u>in adults</u> with clinical outcomes and/or validated laboratory endpoints plus accompanying data <u>in children</u>^a from one or more well-designed, non randomized trials or observational cohort studies with long-term clinical outcomes</p> <p>II: One or more well-designed, nonrandomized trials or observational cohort studies <u>in children</u>^a with long-term clinical outcomes</p> <p>II*: One or more well-designed, nonrandomized trials or observational cohort studies <u>in adults</u> with long-term clinical outcomes plus accompanying data <u>in children</u>^a from one or more smaller nonrandomized trials or cohort studies with clinical outcome data</p> <p>III: Expert opinion</p>

^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 ¹	Pre-Therapy ²	ART Initiation ³	Weeks 1–2 on Therapy	Weeks 2–4 on Therapy	Every 3–4 Months ⁴	Only Required Every 6–12 Months ⁵	ARV Switch
History and Physical	√	√	√	√	√	√		√
Adherence Evaluation		√	√	√	√	√		√
CD4 Count	√	√	√			√		√
Plasma Viral Load	√	√	√		√	√		√
Resistance Testing	√							√
CBC with Differential	√	√	√		√	√		√
Chemistries	√	√	√		√	√		√
Lipid Panel	√		√				√	
Random Plasma Glucose			√				√	
Urinalysis	√		√				√	

¹ See text for details on recommended laboratory tests to obtain.

² 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).

³ If ART is initiated within 30 to 90 days of a pre-therapy lab result, repeat testing may not be necessary.

⁴ CD4 cell count can be monitored less frequently (every 6–12 months) in children and youth who are adherent to therapy and have CD4 cell value well above the threshold for opportunistic infection risk, sustained viral suppression, and stable clinical status for more than 2 to 3 years.

⁵ If lipids have been abnormal in the past, more frequent monitoring might be needed. For patients treated with TDF, more frequent urinalysis is considered.

⁶ When considering starting ARV drugs with activity against hepatitis B, specifically lamivudine-, emtricitabine-, and tenofovir-containing regimens

⁷ Recommended only if individual previously demonstrated no immunity to hepatitis B

Key to Acronyms: ART = antiretroviral therapy, ARV = antiretroviral, CBC = complete blood count, CD4 = CD4 T lymphocyte

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*	0.2–1 mL	0.1–1 mL	1 mL	0.5 mL
Manufacturer	Abbott	bioMerieux	Roche	Siemens

* **Note:** Smaller volumes for children can be accommodated.

Key to Acronyms: 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.

Table 6: HIV-Related Symptoms

Mild HIV-Related Symptoms
Children with 2 or more of the conditions listed but none of the conditions listed in Moderate Symptoms category <ul style="list-style-type: none">• 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
<ul style="list-style-type: none">• Anemia (hemoglobin < 8 g/dL [< 80 g/L]), neutropenia (white blood cell count $< 1,000/\mu\text{L}$ [$< 1.0 \times 10^9/\text{L}$]), and/or thrombocytopenia (platelet count $< 100 \times 10^3/\mu\text{L}$ [$< 100 \times 10^9/\text{L}$]) 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
<ul style="list-style-type: none">• 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• <i>Mycobacterium avium</i> complex or <i>Mycobacterium kansasii</i>, disseminated or extrapulmonary• <i>Mycobacterium tuberculosis</i> of any site, pulmonary, disseminated, or extrapulmonary• <i>Mycobacterium</i>, other species or unidentified species, disseminated or extrapulmonary• <i>Pneumocystis jirovecii</i> (previously known as <i>Pneumocystis carinii</i>) 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 in treatment-naive children generally contains 1 NNRTI **or** 1 PI boosted with ritonavir **or** cobicistat or 1 INSTI **plus** a 2-NRTI backbone. Preferred regimens are so designated based on efficacy, ease of administration and acceptable toxicity. Alternative regimens have also demonstrated efficacy, but have disadvantages compared with preferred regimens in terms of more limited experience in children or less favorable ease of administration. Regimens should be individualized based on advantages and disadvantages of each combination (see [Table 8](#)).

For children who are receiving an effective and tolerable ART regimen, that regimen can be continued as they age even if the combination they are receiving is no longer a preferred regimen.

Preferred Regimens	
Infants, Birth to <14 Days ^{a,b}	2 NRTIs plus NVP
Children Aged ≥14 Days to <2 Years	2 NRTIs plus LPV/r
Children Aged ≥2 Years to <3 Years	2 NRTIs plus LPV/r
	2 NRTIs plus RAL ^c
Children Aged ≥3 Years to <6 Years	2 NRTIs plus ATV/r
	2 NRTIs plus twice-daily DRV/r ^d
	2 NRTIs plus RAL ^c
Children Aged ≥6 Years to <12 Years	2 NRTIs plus ATV/r
	2 NRTIs plus DTG ^e
Adolescents Aged ≥12 Years and Not Sexually Mature (SMR I–III)	2 NRTIs plus ATV/r
	2 NRTIs plus DTG ^e
	2 NRTIs plus once-daily DRV/r ^d
	2 NRTIs plus EVG/ COBI ^f
Adolescents Aged ≥12 Years and Sexually Mature (SMR IV or V)	Refer to Adult and Adolescent Guidelines
Alternative Regimens	
Children Aged >14 Days to <3 Years	2 NRTIs plus NVP ^g
Children Aged ≥4 Weeks to <2 Years and Weighing ≥3 kg	2 NRTIs plus RAL ^c
Children Aged ≥3 Months to <3 Years and Weighing ≥10 kg	2 NRTIs plus ATV/r
Children Aged ≥3 Years to <6 Years	2 NRTIs plus EFV ^h
	2 NRTIs plus LPV/r
Children Aged ≥6 Years to <12 Years	2 NRTIs plus twice-daily DRV/r ^d
	2 NRTIs plus EFV ^h
	2 NRTIs plus LPV/r
	2 NRTIs plus RAL ^c
Adolescents Aged ≥12 Years and Not Sexually Mature (SMR I–III)	2 NRTIs plus EFV ^h
	2 NRTIs plus RAL ^c
	2 NRTIs plus RPV ⁱ
Preferred 2-NRTI Backbone Options for Use in Combination with Additional Drugs	
Children, Birth to <3 Months	ZDV plus (3TC or FTC)

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

Preferred 2-NRTI Backbone Options for Use in Combination with Additional Drugs, continued	
Children Aged ≥3 Months to <12 Years	ABC plus (3TC or FTC)
	ZDV plus (3TC or FTC)
Adolescents Aged ≥12 Years and Not Sexually Mature (SMR I–III)	ABC plus (3TC or FTC)
	TAF plus FTC
Adolescents Aged ≥12 Years and Sexually Mature (SMR IV or V)	Refer to the Adult and Adolescent Guidelines
Alternative 2-NRTI Backbone Options for Use in Combination with Additional Drugs	
Children Aged ≥2 Weeks	ZDV plus ddl
Children Aged ≥3 Months	ZDV plus ABC
Adolescents at SMR III	TDF plus (3TC or FTC)
Adolescents Aged ≥12 Years at SMR III	ZDV plus (3TC or FTC)
2-NRTI Regimens for Use in Special Circumstances in Combination with Additional Drugs	
Children Aged ≥2 Years and Adolescents, SMR I or II	ddl plus (3TC or FTC)
	TDF plus (3TC or FTC)

^a If treatment initiation is planned prior to 14 days of age, NVP is the *Preferred* agent. 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). Consultation with an expert in pediatric HIV infection should be sought. Additional considerations regarding the use of NVP in infants aged <14 days can be located in [Specific Issues in Antiretroviral Therapy in Newborn Infants with HIV Infection](#). A change from NVP to LPV/r should be considered when the infant is aged ≥14 days and 42 weeks post-gestational age, based on infant genotype and the better outcomes of LPV/r in children aged <3 years.

^b LPV/r should not be administered to neonates before a postmenstrual age (first day of the mother’s last menstrual period to birth plus the time elapsed after birth) of 42 weeks and 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 aged 4 weeks to 2 years.

^d DRV once-daily should not be used in children aged <12 years **or weighing <40 kg** or 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 and not sexually mature (SMR I–III) where once-daily administration is possible.

^e DTG is recommended only for children and adolescents **weighing ≥30 kg**.

^f EVG is currently recommended only in fixed-dose combination tablets. Tablets containing EVG/COBI/FTC/TAF are recommended as *Preferred* for children **and adolescents** weighing ≥35 kg. Tablets containing EVG/COBI/FTC/TDF are recommended only for **children and adolescents** weighing ≥35 kg, and in SMR IV or V.

^g NVP should not be used in post-pubertal girls with a CD4 cell count >250/mm³, unless the benefit clearly outweighs the risk. NVP is FDA-approved for treatment of infants aged ≥15 days.

^h ERV is licensed for use in children aged ≥3 months who weigh ≥3.5 kg but is not recommended by the Panel as initial therapy in children aged ≥3 months to 3 years.

ⁱ RPV should be administered to adolescents aged ≥12 years and weighing ≥35 kg who have an initial viral load ≤100,000 copies/mL.

Key to Acronyms: 3TC = lamivudine; ABC = abacavir; ATV = atazanavir; ATV/r = atazanavir/ritonavir; ART = antiretroviral therapy; **COBI=cobicistat**; ddl = didanosine; DRV = darunavir; DRV/r = darunavir/ritonavir; DTG = dolutegravir; EFV = efavirenz; EVG = elvitegravir; FDA = Food and Drug Administration; 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; 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		<u>Integrase Inhibitor Class Advantages:</u> <ul style="list-style-type: none"> • Susceptibility of HIV to a new class of ARV drugs • Few drug-drug interactions • Well-tolerated 	<u>Integrase Inhibitor Class Disadvantages:</u> <ul style="list-style-type: none"> • Limited data on pediatric dosing or safety
	DTG	<ul style="list-style-type: none"> • Once-daily administration • Can give with food • Available as a fixed-dose combination tablet containing ABC/3TC/DTG (Triumeq) in a single, but large, tablet • Single-agent DTG pills are available in several dosages and are small in size 	<ul style="list-style-type: none"> • Drug interactions with EFV, FPV/r, TPV/r, and rifampin necessitating twice-daily dosing
	EVG	<ul style="list-style-type: none"> • Once-daily administration • Available as a fixed-dose combination tablet containing EVG/COBI/FTC/TDF (Stribild) and as a fixed-dose combination tablet containing EVG/COBI/FTC/TAF (Genvoya) 	<ul style="list-style-type: none"> • 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 with normal glomerular clearance.
	RAL	<ul style="list-style-type: none"> • Can give with food. • Available in tablet, chewable tablet, and powder formulations 	<ul style="list-style-type: none"> • Potential for rare systemic allergic reaction or hepatitis
NNRTIs In Alphabetical Order		<u>NNRTI Class Advantages:</u> <ul style="list-style-type: none"> • 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. 	<u>NNRTI Class Disadvantages:</u> <ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • Once-daily administration • Available as a fixed-dose combination tablet containing EFV/FTC/TDF (Atripla) • Potent ARV activity • Can give with food (but avoid high-fat meals). • Capsules can be opened and added to food. 	<ul style="list-style-type: none"> • 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. • Use with caution in adolescent females of childbearing age.
	NVP	<ul style="list-style-type: none"> • 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. 	<ul style="list-style-type: none"> • 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 m²

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	RPV	<ul style="list-style-type: none"> Once-daily dosing Available in a 1-pill-daily, fixed-dose combination tablet containing RPV/FTC/TDF (Complera) and RPV/FTC/TAF (Odefsey) 	<ul style="list-style-type: none"> Should not use in patients with HIV viral load >100,000 copies/mL Low barrier for resistance
PIs In Alphabetical Order		PI Class Advantages: <ul style="list-style-type: none"> NNRTI-sparing Clinical, virologic, and immunologic efficacy are well-documented. Resistance to PIs requires multiple mutations. When combined with dual-NRTI backbone, targets HIV at 2 steps of viral replication (viral reverse transcriptase and protease enzymes). 	PI Class Disadvantages: <ul style="list-style-type: none"> 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 ritonavir boosting resulting in associated drug interactions.
	ATV/r	<ul style="list-style-type: none"> 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). Available in a fixed-dose combination tablet containing ATV/COBI (Evotaz) that reduces pill burden of a boosted PI regimen 	<ul style="list-style-type: none"> 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 large number of drug interactions.
	DRV/r	<ul style="list-style-type: none"> Can be used once daily in children aged ≥ 12 years Liquid formulation available Available in a fixed-dose combination tablet containing DRV/COBI (Prezcobix) that reduces pill burden of a boosted PI regimen. 	<ul style="list-style-type: none"> Pediatric pill burden high with current tablet dose formulations Food effect (should be administered with food) Must be given with RTV boosting to achieve adequate plasma concentrations. Contains sulfa moiety. The potential for cross sensitivity between DRV and other drugs in sulfonamide class is unknown. RTV component associated with large number of drug interactions. Can only be used once-daily in absence of certain PI-associated resistance mutations.
	LPV/r	<ul style="list-style-type: none"> 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. 	<ul style="list-style-type: none"> Poor palatability of liquid formulation (bitter taste), although palatability of combination better than RTV alone. Food effect (liquid formulation should be administered with food). RTV component associated with large number of drug interactions. Should not be administered to neonates before a postmenstrual age (first day of the mother's last menstrual period to birth plus the time elapsed after birth) of 42 weeks and a postnatal age ≥ 14 days. Must be used with caution in patients with preexisting conduction system defects (can prolong PR and QT interval of ECG).

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
Dual-NRTI Backbones In Alphabetical Order	ABC plus (3TC or FTC)	<ul style="list-style-type: none"> Palatable liquid formulations Can give with food. ABC and 3TC are coformulated as a single pill for older/larger patients weighing ≥ 25 kg Available as a fixed-dose combination tablet containing ABC/3TC/DTG (Triumeq) in a single, but large, tablet. 	<ul style="list-style-type: none"> Risk of ABC HSR; perform HLA-B*5701 screening before initiation of ABC treatment.
	ddl plus (3TC or FTC)	<ul style="list-style-type: none"> Delayed-release capsules of ddl may allow once-daily dosing in children aged ≥ 6 years, weighing ≥ 20 kg, able to swallow pills, and who can receive adult dosing along with once-daily FTC. FTC available as a palatable liquid formulation administered once daily. 	<ul style="list-style-type: none"> Food effect (ddl is recommended to be taken 1 hour before or 2 hours after food). Some experts give ddl without regard to food in infants or when adherence is an issue (ddl can be co-administered with FTC or 3TC). Limited pediatric experience using delayed-release ddl capsules in younger children Pancreatitis, lactic acidosis, neurotoxicity with ddl
	TAF plus FTC for adolescents ≥ 12 years	<ul style="list-style-type: none"> Once-daily dosing Small tablet size Less tenofovir-associated renal and bone toxicity with TAF compared to TDF in adults TAF and FTC are coformulated as a single tablet (Descovy). Available as fixed-dose combination tablets: EVG/COBI/FTC/TAF (Genvoya) and RPV/FTC/TAF (Odefsey) 	N/A
	TDF plus (3TC or FTC) for adolescents, SMR IV or V	<ul style="list-style-type: none"> 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 TDF and FTC are coformulated as single tablet (Truvada) and available in multiple strengths. Available as fixed-dose combination tablets: EFV/FTC/TDF (Atripla), EVG/COBI/FTC/TDF (Stribild), and RPV/FTC/TDF (Complera) 	<ul style="list-style-type: none"> 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 ddl, LPV/r, ATV, and TPV.
	ZDV plus (3TC or FTC)	<ul style="list-style-type: none"> Extensive pediatric experience ZDV and 3TC are coformulated as single pill for older/larger patients. Palatable liquid formulations Can give with food. FTC is available as a palatable liquid formulation administered once daily. 	<ul style="list-style-type: none"> Bone marrow suppression with ZDV Lipoatrophy with ZDV
	ZDV plus ABC	<ul style="list-style-type: none"> Palatable liquid formulations Can give with food. 	<ul style="list-style-type: none"> Risk of ABC HSR; perform HLA-B*5701 screening before initiation of ABC treatment Bone marrow suppression and lipoatrophy with ZDV

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	ZDV plus ddl	<ul style="list-style-type: none"> • Extensive pediatric experience • Delayed-release capsules of ddl may allow SMR dosing of ddl in older children able to swallow pills and who can receive adult doses 	<ul style="list-style-type: none"> • Bone marrow suppression and lipodystrophy with ZDV • Pancreatitis, neurotoxicity, lactic acidosis with ddl • ddl liquid formulation is less palatable than 3TC or FTC liquid formulation • Food effect (ddl is recommended to be taken 1 hour before or 2 hours after food). Some experts give ddl without regard to food in infants or when adherence is an issue.

^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 ARV Guidelines](#) for more information.

Key to Acronyms: 3TC = lamivudine; ABC = abacavir; **AE = adverse event**; ARV = antiretroviral; ATV/r = atazanavir/ritonavir; BSA = body surface area; CNS = central nervous system; COBI = cobicistat; DRV/r = darunavir/ritonavir; ddl = didanosine; DTG = dolutegravir; ECG = electrocardiogram; EFV = efavirenz; EVG = elvitegravir; **FPV/r = fosamprenavir/ritonavir**; FTC = emtricitabine; HSR = hypersensitivity reaction; 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; PK = pharmacokinetic; RAL = raltegravir; RPV = rilpivirine; RTV = ritonavir; SJS = Stevens-Johnson Syndrome; SMR = sexual maturity rating; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; TG = triglycerides; **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 for Being Not Recommended
Unboosted ATV -containing regimens in children	Reduced exposure
DRV -based regimens once daily in children ≥ 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 ddl	Insufficient data to recommend
Dual NRTI combination of ABC plus TDF	Insufficient data to recommend
Regimens containing d4T	Increased toxicities
Dual NRTI combination of TDF plus ddl	Increase in concentrations; high rate of virologic failure
EFV -based regimens for children aged <3 years	Appropriate dose not determined
T20 -containing regimens	Insufficient data to recommend Injectable preparation
ETR -based regimens	Insufficient data to recommend
EVG -based regimens	Insufficient data to recommend regimens containing EVG except when administered as the fixed-dose combination tablet containing elvitegravir/cobicistat/emtricitabine/TAF (Genvoya) in adolescents aged 12–18 and weighing ≥ 35 kg (see What to Start)
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 Abbreviations: ABC = abacavir; ARV = antiretroviral; ART = antiretroviral therapy; ATV = atazanavir; d4T = stavudine; ddl = didanosine; DRV = darunavir; EFV = efavirenz; ETR = etravirine; EVG = elvitegravir; 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 = pharmacokinetic; RTV = ritonavir; SQV = saquinavir; T20 = enfuvirtide; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; TPV = tipranavir

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

ART Regimens <u>Never</u> Recommended for Children		
Regimen	Rationale	Exceptions
1 ARV Drug Alone (Monotherapy)	<ul style="list-style-type: none"> • Rapid development of resistance • Inferior antiviral activity compared with combination including ≥3 ARV drugs • Monotherapy “holding” regimens associated with more rapid CD4 decline compared to non-suppressive ART 	<ul style="list-style-type: none"> • Infants exposed to HIV (with negative viral testing) during 4- to 6-week period of prophylaxis to prevent perinatal transmission of HIV
2 NRTIs Alone	<ul style="list-style-type: none"> • Rapid development of resistance • Inferior antiviral activity compared with combination including ≥3 ARV drugs 	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • High rate of early viral failure when this triple-NRTI regimen was used as initial therapy in treatment-naive adults 	<ul style="list-style-type: none"> • No exceptions
TDF plus ddI plus (3TC or FTC) as a Triple-NRTI Regimen	<ul style="list-style-type: none"> • High rate of early viral failure when this triple-NRTI regimen was used as initial therapy in treatment-naive adults 	<ul style="list-style-type: none"> • No exceptions
ARV Components <u>Never</u> Recommended as Part of an ARV Regimen for Children		
Regimen	Rationale	Exceptions
ATV plus IDV	<ul style="list-style-type: none"> • Potential additive hyperbilirubinemia 	<ul style="list-style-type: none"> • No exceptions
Dual-NNRTI Combinations	<ul style="list-style-type: none"> • Enhanced toxicity 	<ul style="list-style-type: none"> • No exceptions
Dual-NRTI Combinations:	<ul style="list-style-type: none"> • Similar resistance profile and no additive benefit 	<ul style="list-style-type: none"> • No exceptions
<ul style="list-style-type: none"> • 3TC plus FTC 		
<ul style="list-style-type: none"> • d4T plus ZDV 	<ul style="list-style-type: none"> • Antagonistic effect on HIV 	<ul style="list-style-type: none"> • No exceptions
NVP as Initial Therapy in Adolescent Girls with CD4 Count >250 cells/mm³ or Adolescent Boys with CD4 Count >400 cells/mm³	<ul style="list-style-type: none"> • Increased incidence of symptomatic (including serious and potentially fatal) hepatic events in these patient groups 	<ul style="list-style-type: none"> • Only if benefit clearly outweighs risk
Unboosted SQV, DRV, or TPV	<ul style="list-style-type: none"> • Poor oral bioavailability • Inferior virologic activity compared with other PIs 	<ul style="list-style-type: none"> • No exceptions

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

Table 11. 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, home visits, or referral to community health nursing.
Targeted Approaches to Monitor Adherence in Special Circumstances	Description
Implement directly observed therapy.	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.	Medication Event Monitoring System [MEMS] caps, Wisepill
Use mobile phone-based technologies.	Interactive voice response, SMS text messaging

^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 Source: 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>.⁴⁴

Table 12. Strategies to Improve Adherence to Antiretroviral Medications

Initial Intervention Strategies
<ul style="list-style-type: none"> • 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 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. • Consider a brief period of hospitalization at start of therapy in selected circumstances for patient education and to assess tolerability of medications chosen.

Table 12. Strategies to Improve Adherence to Antiretroviral Medications

Medication Strategies
<ul style="list-style-type: none">• Choose the simplest regimen possible, reducing dosing frequency 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
<ul style="list-style-type: none">• 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, 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 selected circumstances, during a brief inpatient hospitalization.• Consider gastrostomy tube use in selected circumstances.• Information on other interventions to consider can be found at http://www.cdc.gov/hiv/prevention/research/compendium/ma/complete.html.

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

Table 13a. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Central Nervous System Toxicity (Last updated April 27, 2017; last reviewed April 27, 2017) (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)	<p><u>Onset:</u></p> <ul style="list-style-type: none"> • 1–6 days after starting LPV/r <p><u>Presentation</u></p> <p><i>Neonates/Premature Infants:</i></p> <ul style="list-style-type: none"> • Global CNS depression (e.g., abnormal EEG, altered state of consciousness, somnolence) 	Unknown, rare case reports	<p>Prematurity</p> <p>Low birth weight</p> <p>Age <14 days (whether premature or term)</p>	<p>Avoid use of LPV/r until a postmenstrual age of 42 weeks and a postnatal age ≥14 days.</p>	<p>Discontinue LPV/r; symptoms should resolve in 1–5 days.</p> <p>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).</p>
Neuropsychiatric Symptoms and Other CNS Manifestations	EFV	<p><u>Onset:</u></p> <ul style="list-style-type: none"> • 1–2 days after initiating treatment for many symptoms • Many symptoms subside or diminish by 2–4 weeks, but may persist in a significant proportion of patients. In one report, 37% experienced persistent symptoms at 12 months and in another, half of discontinuations occurred after 12 months. <p><u>Presentation (May Include One or More of the Following)</u></p> <p><i>Neuropsychiatric Symptoms:</i></p> <ul style="list-style-type: none"> • Abnormal dreams • Psychosis • Suicidal ideation or attempted/completed suicide <p><i>Other CNS Manifestations:</i></p> <ul style="list-style-type: none"> • Dizziness • Somnolence • Insomnia or poor sleep quality • Impaired concentration • Seizures (including absence seizures) 	<p>Variable, depending on age, symptom, assessment method</p> <p><u>Children:</u></p> <ul style="list-style-type: none"> • 24% for any EFV-related CNS manifestations in 1 case series with 18% requiring drug discontinuation • 9% incidence of new-onset seizures reported in 1 study in children aged <36 months. In 2 of the children the seizures had alternative causes. • Cases of cerebellar dysfunction have been reported in children in association with very high EFV plasma levels. <p><u>Adults:</u></p> <ul style="list-style-type: none"> • 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. 	<p>Insomnia associated with elevated EFV trough concentration ≥4 mcg/mL</p> <p>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)</p> <p>Prior history of psychiatric illness or use of psychoactive drugs</p>	<p>Administer EFV on an empty stomach, preferably at bedtime.</p> <p>Prescreen for and avoid use in the presence of psychiatric illness including depression or suicidal thoughts or with concomitant use of psychoactive drugs.</p> <p>TDM can be considered in the context of a child with mild or moderate toxicity possibly attributable to a particular ARV agent (see Role of Therapeutic Drug Monitoring in Management of Treatment Failure).</p>	<p>Obtain EFV trough concentration if symptoms excessive or persistent. If EFV trough concentration >4 mcg/mL, strongly consider drug substitution if suitable alternative exists. Alternatively, consider dose reduction with repeat TDM and dose adjustment (with expert pharmacologist input).</p> <p>In a small study, cyproheptadine was shown to reduce short-term incidence of neuropsychiatric effects in adults receiving EFV, but data are lacking in children and no recommendation can be made for its use at this time.</p>

Table 13a. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Central Nervous System Toxicity (Last updated April 27, 2017; last reviewed April 27, 2017) (page 2 of 3)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/Monitoring	Management
Neuropsychiatric Symptoms and Other CNS Manifestations	EFV	<ul style="list-style-type: none"> Cerebellar dysfunction (tremor, dysmetria, ataxia) <p>Note: Some CNS side effects (e.g., impaired concentration, abnormal dreams, or sleep disturbances) may be more difficult to assess in children.</p>				
	RPV	<p><u>Presentation</u></p> <p><i>Neuropsychiatric Symptoms:</i></p> <ul style="list-style-type: none"> Depressive disorders Suicidal ideation Abnormal dreams/nightmares <p><i>Other CNS Manifestations:</i></p> <ul style="list-style-type: none"> Headache Dizziness Insomnia Somnolence 	<p><u>In Adults:</u></p> <ul style="list-style-type: none"> 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. <p><u>In Children:</u></p> <ul style="list-style-type: none"> Depressive disorders of all severity grades were reported in 19.4% of pediatric patients aged 12 years to 17 years. Severe depressive disorders were reported in 5.6% of patients, including a suicide attempt in 1 subject. Somnolence reported in 5/36 (14%) children. 	Prior history of neuropsychiatric illness	Monitor carefully for depressive disorders and other CNS symptoms.	Consider drug substitution in case of severe symptoms.
	RAL	<p><u>Presentation:</u></p> <ul style="list-style-type: none"> Increased psychomotor activity Headaches Insomnia Depression Cerebellar dysfunction (e.g., tremor, dysarthria, ataxia) 	<p><u>Children:</u></p> <ul style="list-style-type: none"> Increased psychomotor activity reported in one child. <p><u>Adults:</u></p> <ul style="list-style-type: none"> Headache Insomnia (<5% in adult trials) Rare case reports of cerebellar dysfunction in adults 	<p>Elevated RAL concentrations</p> <p>Co-treatment with TDF or PPI or inhibitors of UGT1A1</p> <p>Prior history of insomnia or depression</p>	<p>Prescreen for psychiatric symptoms.</p> <p>Monitor carefully for CNS symptoms.</p> <p>Use with caution in the presence of drugs that increase RAL concentration.</p>	Consider drug substitution (RAL or co-administered drug) in case of severe insomnia or other neuropsychiatric symptoms.

Table 13a. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Central Nervous System Toxicity (Last updated April 27, 2017; last reviewed April 27, 2017) (page 3 of 3)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/Monitoring	Management
	DTG	<p><u>Onset:</u></p> <ul style="list-style-type: none"> • 7–30 days after initiating drug <p><u>Presentation</u></p> <p><i>Neuropsychiatric Symptoms:</i></p> <ul style="list-style-type: none"> • Depression or exacerbation of preexisting depression • Anxiety • Suicidal ideation attempt, behavior, or completion <p><i>Other CNS Manifestations (Generally Mild):</i></p> <ul style="list-style-type: none"> • Insomnia • Dizziness • Headache 	<p><u>Adults:</u></p> <ul style="list-style-type: none"> • Exact frequency of neuropsychiatric symptoms is unknown; case reports of 4 adult patients. Headache, insomnia, and dizziness are common, reported in up to 10% of patients. Less than 1% of patients experienced more severe symptoms. 	Pre-existing depression or other psychiatric illness	Use with caution in the presence of psychiatric illness, especially depression.	<p>For severe neuropsychiatric symptoms, consider discontinuation of DTG if suitable alternative exists.</p> <p>Discontinuation resulted in resolution of neuropsychiatric symptom in 3 out of 4 patients (in the fourth patient, symptoms resolved slowly despite DTG continuation).</p> <p>For mild symptoms, continue DTG and counsel patient that symptoms will likely resolve with time.</p>
Intracranial Hemorrhage	TPV	<p><u>Onset:</u></p> <ul style="list-style-type: none"> • 7–513 days after starting TPV 	<p><u>Children:</u></p> <ul style="list-style-type: none"> • No cases of ICH reported in children. <p><u>Adults:</u></p> <ul style="list-style-type: none"> • 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 present in most patients in case series reported.	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: ARV = antiretroviral; ATV = atazanavir; CNS = central nervous system; CYP = cytochrome P; DTG = dolutegravir; EEG = electroencephalogram; EFV = efavirenz; ICH = intracranial hemorrhage; LPV/r = ritonavir-boosted lopinavir; 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 13b. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Dyslipidemia

(Last updated April 27, 2017; last reviewed April 27, 2017) (page 1 of 2)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/Monitoring	Management
Dyslipidemia	<p>PIs:</p> <ul style="list-style-type: none"> All PIs, especially RTV-boosted PIs; lower incidence reported with DRV/r and ATV with or without RTV. <p>NRTIs:</p> <ul style="list-style-type: none"> Especially d4T <p>NNRTIs:</p> <ul style="list-style-type: none"> EFV > NVP, RPV, and ETR 	<p>Onset:</p> <ul style="list-style-type: none"> As early as 2 weeks to months after beginning therapy <p>Presentation</p> <p>PIs:</p> <ul style="list-style-type: none"> ↑LDL-C, TC, and TG <p>NNRTIs:</p> <ul style="list-style-type: none"> ↑LDL-C, TC, and HDL-C <p>NRTIs:</p> <ul style="list-style-type: none"> ↑LDL-C, TC, and TG 	<p>Reported frequency varies with specific ARV regimen, duration of ART and specific laboratory parameters used to diagnose lipid abnormalities.</p> <p>10% to 20% in young children receiving LPV/RTV.</p> <p>40% to 75% of older children and adolescents with prolonged ART history will have lipid abnormalities.</p> <p>Higher abnormal fasting serum lipids in EVG/COBI/FTC/TAF vs. EVG/COBI/FTC/TDF regimen in studies of treatment-naïve adults</p> <p>Increase in serum lipids from baseline also noted in adolescents receiving EVG/COBI/FTC/TAF</p>	<p>Advanced-stage HIV disease</p> <p>High-fat, high-cholesterol diet</p> <p>Lack of exercise</p> <p>Obesity</p> <p>Hypertension</p> <p>Smoking</p> <p>Family history of dyslipidemia or premature CVD</p> <p>Metabolic syndrome</p> <p>Fat maldistribution</p>	<p>Prevention:</p> <ul style="list-style-type: none"> Low-fat diet Exercise Smoking-prevention counseling Avoid d4T <p>Monitoring^a</p> <p>Adolescents and Adults:</p> <ul style="list-style-type: none"> 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. <p>Children (Aged ≥2 Years) without Lipid Abnormalities or Additional Risk Factors:</p> <ul style="list-style-type: none"> Obtain non-fasting 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. <p>Children with Lipid Abnormalities and/or Additional Risk Factors:</p> <ul style="list-style-type: none"> Obtain 12-hour FLP before initiating or changing therapy and every 6 months thereafter (more often if indicated). 	<p>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</p> <p>Counsel on lifestyle modification, dietary interventions (e.g., a diet low in saturated fat, cholesterol, and refined sugars particularly in case of ↑TG, elimination of transfat, physical activity, smoking cessation) for an adequate trial period (3–6 months). Consider consultation with dietician.</p> <p>ART regimen changes can be considered. Discontinue d4T or substitute a PI-sparing regimen or PI-based regimen with a more favorable lipid profile.</p> <p>Consider lipid-lowering therapy in consultation with a lipid specialist if ≥6-month trial of lifestyle modification fails.</p> <p>Some experts suggest treatment in 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</p> <p>The minimal goal of therapy should be to achieve and maintain a LDL-C value below 130 mg/dL, while maintaining viral control.</p>

Table 13b. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Dyslipidemia

(Last updated April 27, 2017; last reviewed April 27, 2017) (page 2 of 2)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/Monitoring	Management
Dyslipidemia, continued					<p><i>Children Receiving Lipid-Lowering Therapy with Statins or Fibrates:</i></p> <ul style="list-style-type: none"> • Obtain 12-hour FLP, LFTs, and CK at 4 and 8 weeks, and 3 months after starting lipid therapy. • 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. 	<p>Statins such as pravastatin, atorvastatin, or rosuvastatin^c can be considered.^d 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 diabetes mellitus. Risks must be weighed against potential benefits. Cholesterol absorption inhibitors (e.g., ezetimibe) can be considered as alternative.</p> <p>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.</p> <p>The long-term risks of lipid abnormalities in children receiving ART are unclear. However, persistent dyslipidemia in children may lead to premature CVD.</p>

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

^b Refer to NHLBI guidelines at http://www.nhlbi.nih.gov/guidelines/cvd_ped/summary.htm#chap9.

^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 (potentially teratogenic) and should not be used in patients who may become pregnant. Multiple drug interactions exist between ARV drugs and statins (exception 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 [Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents](#).

Key to Acronyms: ALT = alanine aminotransferase; ART = antiretroviral therapy; ARV = antiretroviral; AST = aspartate aminotransferase; ATV = atazanavir; CK = creatine kinase; CVD = cardiovascular disease; CYP3A4 = cytochrome P450 3A4; d4T = stavudine; DRV = darunavir; DRV/r = ritonavir-boosted darunavir; EFV = efavirenz; ETR = etravirine; FLP = fasting lipid profile; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; LFT = liver function test; LPV = lopinavir; 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; TC = total cholesterol; TG = triglyceride

Table 13c. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Gastrointestinal Effects (Last updated April 27, 2017; last reviewed April 27, 2017)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/Monitoring	Management
Nausea/Vomiting	Principally ZDV and PIs, but can occur with all ARVs and COBI	<u>Onset:</u> • Early <u>Presentation:</u> • 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.	Reassurance—generally improves over time (usually 6–8 weeks) Supportive care. Antiemetics may be useful in extreme or persistent cases.
Diarrhea	PIs (particularly NFV, LPV/r, FPV/r), buffered ddI, INSTIs (mild)	<u>Onset:</u> • Early <u>Presentation:</u> • Generally soft, more frequent stools	Varies with ARV agent; 10% to 30% in some series	Unknown	Monitor for weight loss, dehydration.	Exclude infectious causes of diarrhea if prolonged or severe. Reassurance—generally improves over time (usually 6–8 weeks) Although treatment data in children are lacking, potentially useful modalities include: • Dietary modification • Calcium carbonate (should not be used with DTG) • Bulk-forming agents (psyllium) • Antimotility agents (loperamide) • Crofelemer is FDA-approved for treatment of ART-associated diarrhea in adults, but not in children .
Pancreatitis	ddI, d4T (especially concurrently), boosted PIs Reported, albeit rarely, with most ARVs.	<u>Onset:</u> • Any time, usually after months of therapy <u>Presentation:</u> • 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	Avoid use of ddI in patients with a history of pancreatitis.	Discontinue offending agent—avoid reintroduction. Manage symptoms of acute episode. If associated with hypertriglyceridemia, consider interventions to lower TG levels.

Key to Acronyms: ART = antiretroviral therapy; ARV = antiretroviral; COBI = cobicistat; d4T = stavudine; ddI = didanosine; DTG = dolutegravir; FDA = Food and Drug Administration; FPV/r = fosamprenavir/ritonavir; INSTI = integrase strand transfer inhibitor; LPV/r = lopinavir/ritonavir; NFV = nelfinavir; PI = protease inhibitor; RTV = ritonavir; TDF = tenofovir disoproxil fumarate; TG = triglyceride; TMP-SMX = trimethoprim sulfamethoxazole; ZDV = zidovudine

Table 13d. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Hematologic Effects (Last updated April 27, 2017; last reviewed April 27, 2017) (page 1 of 2)

Adverse Effects	Associated ARVs	Onset/ Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
Anemia^a	ZDV	<p><u>Onset:</u></p> <ul style="list-style-type: none"> • Variable, weeks to months <p><u>Presentation</u></p> <p><i>Most Commonly:</i></p> <ul style="list-style-type: none"> • Asymptomatic or mild fatigue • Pallor • Tachypnea <p><i>Rarely:</i></p> <ul style="list-style-type: none"> • Congestive heart failure 	<p><u>Newborns Exposed to HIV:</u></p> <ul style="list-style-type: none"> • Severe anemia is uncommon, but may be seen coincident with physiologic Hgb nadir. <p><u>Children Living with HIV on ARVs:</u></p> <ul style="list-style-type: none"> • 2–3 times more common with ZDV-containing regimens 	<p><u>Newborns Exposed to HIV:</u></p> <ul style="list-style-type: none"> • Premature birth • <i>In utero</i> exposure to ARVs • Advanced maternal HIV • Neonatal blood loss • Combination ARV prophylaxis, particularly with ZDV plus 3TC <p><u>Children Living with HIV on ARVs:</u></p> <ul style="list-style-type: none"> • 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 	<p><u>Newborns Exposed to HIV:</u></p> <ul style="list-style-type: none"> • 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). <p><u>Children Living with HIV on ARVs:</u></p> <ul style="list-style-type: none"> • Avoid ZDV in children with moderate to severe anemia when alternative agents are available. • Obtain CBC as part of routine care. 	<p><u>Newborns Exposed to HIV:</u></p> <ul style="list-style-type: none"> • Rarely requires intervention unless Hgb is <7.0 g/dL or is associated with symptoms. • Consider discontinuing ZDV if 4 weeks or more of prophylaxis has been completed (see the Perinatal Guidelines^b). <p><u>Children Living with HIV on ARVs:</u></p> <ul style="list-style-type: none"> • Discontinue non-ARV, marrow-toxic drugs, if feasible. • Treat coexisting iron deficiency, OIs, malignancies. • For persistent severe anemia thought to be associated with ARVs, change to a non-ZDV-containing regimen
Macrocytosis	ZDV; also d4T	<p><u>Onset:</u></p> <ul style="list-style-type: none"> • Within days to weeks of starting therapy • MCV often >100 fL <p><u>Presentation:</u></p> <ul style="list-style-type: none"> • Most often asymptomatic. • Sometimes associated with anemia (occurs more often with ZDV than with d4T). 	>90% to 95%, all ages	None	Obtain CBC as part of routine care (see Laboratory and Clinical Monitoring section).	None required unless associated with anemia. D4T is no longer recommended and should be discontinued.

Table 13d. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Hematologic Effects (Last updated April 27, 2017; last reviewed April 27, 2017) (page 2 of 2)

Adverse Effects	Associated ARVs	Onset/ Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
Neutropenia ^a	ZDV	<p>Onset:</p> <ul style="list-style-type: none"> • Variable <p>Presentation:</p> <ul style="list-style-type: none"> • Most commonly asymptomatic. 	<p><u>Newborns Exposed to HIV:</u></p> <ul style="list-style-type: none"> • Rare <p><u>Children Living with HIV on ARVs:</u></p> <ul style="list-style-type: none"> • 2.2% to 26.8% of children on ARVs, depending upon the ARV regimen. 2.2% for ZDV/3TC • Highest rates with ZDV-containing regimens. 	<p><u>Newborns Exposed to HIV:</u></p> <ul style="list-style-type: none"> • <i>In utero</i> exposure to ARVs • Combination ARV prophylaxis, particularly with ZDV plus 3TC <p><u>Children Living with HIV on ARVs:</u></p> <ul style="list-style-type: none"> • Advanced or poorly controlled HIV infection • Myelosuppressive drugs (e.g., TMP-SMX, ganciclovir, hydroxyurea, rifabutin) 	<p><u>Children Living with HIV on ARVs:</u></p> <ul style="list-style-type: none"> • Obtain CBC as part of routine care. 	<p><u>Newborns Exposed to HIV:</u></p> <ul style="list-style-type: none"> • No established threshold for intervention; some experts would consider using an alternative NRTI for prophylaxis if ANC <500 cells/mm³, or discontinue prophylaxis if ≥4 weeks of ZDV have been completed (see the Perinatal ARV Guidelines^b). <p><u>Children Living with HIV on ARVs:</u></p> <ul style="list-style-type: none"> • 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 non-ZDV-containing regimen.

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

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

Key to Acronyms: 3TC = lamivudine; ANC = absolute neutrophil count; ARV = antiretroviral; CBC = complete blood count; d4t = stavudine; 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 13e. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Hepatic Events

(Last updated April 27, 2017; last reviewed April 27, 2017) (page 1 of 2)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/Monitoring	Management
Hepatitis	<ul style="list-style-type: none"> • 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 all been associated with hepatitis in context of hypersensitivity reactions • NRTIs (especially ZDV, ddI, and d4T) have been associated with lactic acidosis and hepatic steatosis 	<p><u>Onset:</u></p> <ul style="list-style-type: none"> • 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 of, withdrawal of, or development of resistance to 3TC, FTC, or TDF (especially if receiving only 1 anti-HBV agent). • Hepatitis may represent IRIS early in therapy, especially in patients with HBV- and HCV-coinfection. <p><u>Presentation:</u></p> <ul style="list-style-type: none"> • Asymptomatic elevation of AST and ALT • Symptomatic hepatitis with nausea, fatigue, and jaundice • Hepatitis may present in context of hypersensitivity reaction with rash, lactic acidosis, and hepatic steatosis. 	Uncommon	<p>HBV or HCV coinfection</p> <p>Other underlying liver disease</p> <p>Use of other hepatotoxic medications (e.g., St. John's wort [<i>Hypericum perforatum</i>], Chaparral [<i>Larrea tridentate</i>], Germander [<i>Teucrium chamaedrys</i>])</p> <p>Alcohol use</p> <p>Pregnancy</p> <p><u>For NVP-Associated Hepatic Events in Adults:</u></p> <ul style="list-style-type: none"> • Female with pre-NVP CD4 count >250 cells/mm³ • Male with pre-NVP CD4 count >400 cells/mm³ • Population- specific HLA types^a • Higher drug concentrations for PIs, particularly TPV. 	<p><u>Prevention:</u></p> <ul style="list-style-type: none"> • Avoid concomitant use of hepatotoxic medications. • If hepatic enzymes are elevated >5 to 10 times ULN or chronic liver disease, most clinicians would avoid NVP. <p><u>Monitoring:</u></p> <p><i>For ARVs Other Than NVP:</i></p> <ul style="list-style-type: none"> • Obtain AST and ALT at baseline and thereafter at least every 3–4 months, or more frequently in at-risk patients (e.g., HBV- or HCV-coinfection or elevated baseline AST and ALT). <p><i>For NVP:</i></p> <ul style="list-style-type: none"> • Obtain AST and ALT at baseline, at 2 and 4 weeks, and then every 3 months. 	<ul style="list-style-type: none"> • Evaluate for other infectious and non-infectious causes and monitor closely. <p><u>Asymptomatic:</u></p> <ul style="list-style-type: none"> • Potentially offending ARVs should be discontinued if ALT or AST is > 5x ULN <p><u>Symptomatic:</u></p> <ul style="list-style-type: none"> • Discontinue all ARVs and other potentially hepatotoxic drugs. <p>If a patient experiences hepatitis attributed to NVP, it should be permanently discontinued.</p> <ul style="list-style-type: none"> • Consider viral causes of hepatitis: HAV, HBV, HCV, EBV, and CMV.

Table 13e. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Hepatic Events
 (Last updated April 27, 2017; last reviewed April 27, 2017) (page 2 of 2)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/Monitoring	Management
Indirect Hyperbilirubinemia	IDV, ATV (with either RTV or COBI)	<p><u>Onset:</u></p> <ul style="list-style-type: none"> • First months of therapy <p><u>Presentation:</u></p> <ul style="list-style-type: none"> • May be associated with jaundice or asymptomatic • 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 > 5x ULN and 1.4% experienced jaundice.	N/A	<p><u>Monitoring:</u></p> <ul style="list-style-type: none"> • No ongoing monitoring needed. After an initial rise over the first few months of therapy, unconjugated bilirubin levels generally stabilize; in some patients, levels improve over time. 	<ul style="list-style-type: none"> • Isolated indirect hyperbilirubinemia is not indication for cessation of potentially offending ARV • Psychological impact of jaundice should be evaluated and alternative agents considered
Non-Cirrhotic Portal Hypertension	ddl, d4T	<p><u>Onset:</u></p> <ul style="list-style-type: none"> • Generally after years of therapy <p><u>Presentation:</u></p> <ul style="list-style-type: none"> • GI bleeding, esophageal varices, hypersplenism • Mild elevations in AST and ALT, moderate increases in ALP, and pancytopenia (because of hypersplenism) • Liver biopsy may reveal a variety of findings, most commonly nodular regenerative hyperplasia or hepatoportal sclerosis. 	Rare	Prolonged exposure to ARV therapy, especially ddl and the combination of ddl and d4T	<p><u>Monitoring:</u></p> <ul style="list-style-type: none"> • No specific monitoring 	<ul style="list-style-type: none"> • 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.

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; ddl = didanosine; EBV = Epstein-Barr virus; EFV = efavirenz; FTC = emtricitabine; GI = gastrointestinal; HAV = hepatitis A virus; HBV = hepatitis B virus; HCV = hepatitis C virus; HLA = human leukocyte antigen; IDV = indinavir; IRIS = immune reconstitution inflammatory syndrome; MVC = maraviroc; NRTI = nucleoside reverse transcriptase inhibitor; NVP = nevirapine; PI = protease inhibitor; RAL = raltegravir; RTV = ritonavir; TDF = tenofovir disoproxil fumarate; TPV = tipranavir; ULN = upper limit of normal; ZDV = zidovudine

Table 13f. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Insulin Resistance, Asymptomatic Hyperglycemia, Diabetes Mellitus (Last updated April 27, 2017; last reviewed April 27, 2017)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/Monitoring	Management
Insulin Resistance, Asymptomatic Hyperglycemia, DM^a	ZDV d4T ddl LPV/r IDV 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)	Insulin Resistance <i>ARV-Treated Children:</i> • 6% to 12% Impaired Fasting Glucose <i>ARV-Treated Children:</i> • 0% to 7% Impaired Glucose Tolerance <i>ARV-Treated Children:</i> • 3% to 4% DM <i>ARV-Treated Children:</i> • 0.2 per 100-person-years	Risk Factors for Type 2 DM: • Lipodystrophy • Metabolic syndrome • Family history of DM • High BMI (obesity)	Prevention: • Lifestyle modification • Avoid ZDV, d4T, ddl when possible. Monitoring: • Monitor for signs of DM, change in body habitus, acanthosis nigricans. <i>Obtain RPG Levels at:</i> • Initiation of ARV therapy • 3–6 months after therapy initiation • Once a year thereafter <i>For RPG ≥ 140 mg/dL:</i> • 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, transfat, and refined sugars; increased physical activity; cessation of smoking); consultation with dietician. Change NRTI backbone (e.g., from ZDV, d4T, or ddl to TAF , TDF, or ABC). <u>For Either RPG ≥ 200 mg/dL plus Symptoms of DM or FPG ≥ 126 mg/dL:</u> • Patient meets diagnostic criteria for DM; consult endocrinologist. <u>FPG 100–125 mg/dL:</u> Impaired FPG is suggestive of insulin resistance; consult endocrinologist. <u>FPG < 100 mg/dL:</u> <i>Normal FPG, but Does Not Exclude Insulin Resistance:</i> • 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 random and fasting plasma glucose levels.

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

Table 13g. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Lactic Acidosis

(Last updated April 27, 2017; last reviewed April 27, 2017)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/Monitoring	Management
Lactic Acidosis	NRTIs, in particular, d4T and ddI (highest risk when co-administered)	<p>Onset:</p> <ul style="list-style-type: none"> 1–20 months after starting therapy (median onset 4 months in 1 case series) <p>Presentation <i>Usually Insidious Onset of a Combination of Signs and Symptoms:</i></p> <ul style="list-style-type: none"> Generalized fatigue, weakness, and myalgias Vague abdominal pain, weight loss, unexplained nausea or vomiting Dyspnea Peripheral neuropathy <p>Note: Patients may present with acute multi-organ failure (e.g., fulminant hepatic, pancreatic, respiratory failure).</p>	<p>Chronic, Asymptomatic Mild Hyperlactatemia (2.1–5.0 mmol/L)</p> <p>Adults:</p> <ul style="list-style-type: none"> 15% to 35% of adults receiving NRTI therapy for longer than 6 months <p>Children:</p> <ul style="list-style-type: none"> 29% to 32% <p>Symptomatic Severe Hyperlactatemia (>5.0 mmol/L)</p> <p>Adults:</p> <ul style="list-style-type: none"> 0.2% to 5.7% <p>Symptomatic Lactic Acidosis/Hepatic Steatosis:</p> <ul style="list-style-type: none"> Rare in all age groups (1.3–11 episodes per 1000 person-years; increased incidence with the use of d4T/ddI when co-administered), but associated with a high fatality rate (33% to 58%) 	<p>Adults:</p> <ul style="list-style-type: none"> Female gender 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/mm³ Acquired riboflavin or thiamine deficiency Possibly pregnancy <p>Preterm Infants or Any Neonates before Post-Menstrual Age of 42 Weeks and a Postnatal Age of ≥14 Days has Been Attained:</p> <ul style="list-style-type: none"> Exposure to propylene glycol (e.g., present as a diluent in LPV/r oral solution) due to diminished ability to metabolize propylene glycol, thereby leading to accumulation and potential adverse events. 	<p>Prevention:</p> <ul style="list-style-type: none"> d4T and ddI should both be avoided individually; co-administration of d4T and ddI is contraindicated (no exception). 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. <p>Monitoring <i>Asymptomatic:</i></p> <ul style="list-style-type: none"> Measurement of serum lactate is not recommended. <p><i>Clinical Signs or Symptoms Consistent with Lactic Acidosis:</i></p> <ul style="list-style-type: none"> 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. 	<p>Lactate 2.1–5.0 mmol/L (Confirmed with Second Test):</p> <ul style="list-style-type: none"> Replace ddI and d4T with other ARVs. As an alternative, temporarily discontinue all ARVs while conducting additional diagnostic workup. <p>Lactate >5.0 mmol/L (Confirmed with Second Test)^b or >10.0 mmol/L (Any 1 Test):</p> <ul style="list-style-type: none"> 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). <p>Anecdotal (Unproven) Supportive Therapies:</p> <ul style="list-style-type: none"> Bicarbonate infusions, THAM, high-dose thiamine and riboflavin, oral antioxidants (e.g., L-carnitine, co-enzyme Q10, vitamin C) <p>Following resolution of clinical and laboratory abnormalities, resume therapy, either with an NRTI-sparing regimen or a revised NRTI-containing regimen instituted with caution, using NRTIs less likely to inhibit mitochondria (ABC or TDF preferred; possibly FTC or 3TC), and monthly monitoring of lactate for at least 3 months.</p>

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

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

Key to 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; TDF = tenofovir disoproxil fumarate; THAM = tris (hydroxymethyl) aminomethane

Table 13h. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Lipodystrophy, Lipohypertrophy, Lipoatrophy (Last updated April 27, 2017; last reviewed April 27, 2017) (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.	<u>Onset:</u> <ul style="list-style-type: none"> Trunk and limb fat initially increase; peripheral fat wasting may not appear for 12 to 24 months after ART initiation. 	Varies greatly depending upon measure and comparator group. <u>Adults:</u> <ul style="list-style-type: none"> Up to 93% <u>Children:</u> <ul style="list-style-type: none"> Up to 34% 	Genetic predisposition Puberty HIV-associated inflammation Older age Longer duration of ART Body habitus	See below.	See below. A regimen review with consideration of changing the regimen should be considered, whenever present. Improvement following regimen change is variable, may take months to several years, or may not occur at all.
Central Lipohypertrophy or Lipoaccumulation	Can occur in the absence of ART, but most associated with PIs and EFV.	<u>Presentation:</u> <ul style="list-style-type: none"> 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. 	<u>Adults:</u> <ul style="list-style-type: none"> Up to 93% <u>Children:</u> <ul style="list-style-type: none"> Up to 27% 	Obesity before initiation of therapy Sedentary lifestyle	<u>Prevention:</u> <ul style="list-style-type: none"> Calorically appropriate low-fat diet and exercise <u>Monitoring:</u> <ul style="list-style-type: none"> BMI measurement Body circumference and waist-hip ratio 	Calorically appropriate healthy diet low in saturated fats and simple carbohydrates, and exercise, especially strength training Smoking cessation (if applicable) to decrease future CVD risk Consider switching from PIs and EFV to an INSTI. <u>Data are Insufficient to Allow the Panel to Safely Recommend Use of Any of the Following Modalities in Children:</u> <ul style="list-style-type: none"> Recombinant human growth hormone Growth hormone-releasing hormone Metformin Thiazolidinediones Recombinant human leptin Anabolic steroids Liposuction

Table 13h. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Lipodystrophy, Lipohypertrophy, Lipoatrophy (Last updated April 27, 2017; last reviewed April 27, 2017) (page 1 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)	<p><u>Presentation:</u></p> <ul style="list-style-type: none"> • Thinning of subcutaneous fat in face, buttocks, and extremities, measured as decrease in trunk/limb fat by DXA or triceps skinfold thickness. Preservation of lean body mass distinguishes lipoatrophy from HIV-associated wasting. 	<p><u>Adults:</u></p> <ul style="list-style-type: none"> • Up to 59% <p><u>Children:</u></p> <ul style="list-style-type: none"> • Up to 47% • Risk lower (up to 15%) in patients not treated with d4T or ZDV. 	Underweight before ART	<p><u>Prevention:</u></p> <ul style="list-style-type: none"> • Avoid use of d4T and ZDV. <p><u>Monitoring:</u></p> <ul style="list-style-type: none"> • Patient self-report and physical exam are the most sensitive methods of monitoring lipoatrophy. 	<p>Replace d4T (no longer recommended) or ZDV with other NRTIs if possible.</p> <p><u>Data are Insufficient to Allow the Panel to Safely Recommend Use of Any of the Following Modalities in Children:</u></p> <ul style="list-style-type: none"> • 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 13i. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Nephrotoxic Effects

(Last updated April 27, 2017; last reviewed April 27, 2017) (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 is not associated with nephrolithiasis.	<u>Onset:</u> <ul style="list-style-type: none"> Weeks to months after starting therapy <u>Clinical Findings:</u> <ul style="list-style-type: none"> Crystalluria, hematuria, pyuria, flank pain, sometimes increased creatinine 	ATV-related nephrolithiasis occurs in <10%. IDV-related higher (29%) in children than adults (12.4%)	In adults, elevated urine pH (>5.7) Unknown in children	<u>Prevention:</u> <ul style="list-style-type: none"> Maintain adequate hydration. IDV is not FDA-approved for use in children and should be avoided. <u>Monitoring:</u> <ul style="list-style-type: none"> Obtain urinalysis at least every 6–12 months. 	Provide adequate hydration and pain control; consider using alternative ARV. If on IDV, discontinue.
Renal Dysfunction	TDF	<u>Onset:</u> <ul style="list-style-type: none"> Variable; in adults, weeks to months after initiation of therapy. Hypophosphatemia appears at a median of 18 months. Glucosuria may have onset after a year of therapy. Abnormal urine protein/osmolality ratio may be an early indicator. <u>Presentation:</u> <i>More Common:</i> <ul style="list-style-type: none"> Increased serum creatinine, proteinuria, normoglycemic glucosuria. Hypophosphatemia, usually asymptomatic; may present with bone and muscle pain, weakness. <i>Less Common:</i> <ul style="list-style-type: none"> Renal failure, acute tubular necrosis, Fanconi syndrome, proximal renal tubulopathy, interstitial nephritis, nephrogenic diabetes insipidus with polyuria 	<u>Adults:</u> <ul style="list-style-type: none"> Approximately 2% with increased serum creatinine Approximately 0.5% with severe renal complications <u>Children:</u> <ul style="list-style-type: none"> Approximately 4% with hypophosphatemia or proximal tubulopathy; higher with prolonged TDF therapy, in advanced HIV infection or concomitant use of ddI 	<u>Risk May Be Increased in Children with:</u> <ul style="list-style-type: none"> Age >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 and 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. In the presence of persistent proteinuria or glucosuria, or for symptoms of bone pain or muscle pain or weakness, also measure serum phosphate. Because toxicity risk increases with duration of TDF treatment, frequency of monitoring should not decrease with time.	If TDF is the likely cause, consider using alternative ARV. TAF has significantly less toxicity than TDF.

Table 13i. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Nephrotoxic Effects

(Last updated April 27, 2017; last reviewed April 27, 2017) (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	<p><u>Onset:</u></p> <ul style="list-style-type: none"> • Within a month of starting treatment <p><u>Presentation:</u></p> <ul style="list-style-type: none"> • Asymptomatic. These drugs decrease renal tubular secretion of creatinine, leading to an increase in measured serum creatinine without a true change in eGFR. 	<p>Common</p> <p>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.</p>	N/A	Monitor serum creatinine. Assess for renal dysfunction if serum creatinine increases by >0.4 mg/dL or increases are ongoing with time.	<p>No need to change therapy.</p> <p>Reassure patient about the benign nature of the laboratory abnormality.</p>

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

Table 13j. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Osteopenia and Osteoporosis (Last updated April 27, 2017; last reviewed April 27, 2017)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/Monitoring	Management
Osteopenia and Osteoporosis	Any ART regimen <u>Specific Agents of Possible Concern:</u> • TDF • PIs, especially LPV/r	<u>Onset:</u> • Any age; decrease in BMD usually seen early after initiation of ART. <u>Presentation:</u> • Most commonly asymptomatic • Rarely presents as osteoporosis; a clinical diagnosis defined by evidence of bone fragility (e.g., fracture with minimal trauma).	<u>BMD z Score Less Than -2.0:</u> • <10% in U.S. cohorts • Approximately 20% to 30% in international cohorts	Longer duration and greater severity of HIV disease Growth or pubertal delay Low BMI Lipodystrophy Non-black race Smoking Prolonged systemic corticosteroid use Medroxyprogesterone use Limited weight-bearing exercise	<u>Prevention:</u> • 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). <u>Monitoring:</u> • Assess nutritional intake (calcium, vitamin D, and total calories). • Consider measuring serum 25-OH-vitamin D level. ^a • DXA. ^b	Same options as for prevention. Consider change in ARV regimen (e.g., changing TDF to TAF). Role of bisphosphonates not established in children with HIV infection.

^a Some experts would periodically measure 25-OH-vitamin D, especially in urban youth with HIV infection, because in that population, the prevalence of vitamin D insufficiency is high.

^b Until more data are available about the long-term effects of TDF on bone mineral acquisition in childhood, some experts would obtain a DXA at baseline and every 6 to 12 months for prepubertal children and children in early puberty who are initiating treatment with TDF. DXA could also be considered in adolescent women on TDF and medroxyprogesterone and in 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; LPV/r = lopinavir/ritonavir; PI = protease inhibitor; TDF = tenofovir disoproxil fumarate, TAF= tenofovir alafenamide

Table 13k. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Peripheral Nervous System Toxicity (Last updated April 27, 2017; last reviewed April 27, 2017)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency ^a	Risk Factors	Prevention/Monitoring	Management
ARV Toxic Neuropathy^b	d4T, ddl PIs	<p><u>Onset:</u> Weeks to months</p> <p><u>Presentation:</u></p> <ul style="list-style-type: none"> • Decreased sensation • Aching, burning, painful numbness • Hyperalgesia • Allodynia • Decreased or absent ankle reflexes <p><u>Distribution:</u></p> <ul style="list-style-type: none"> • Bilateral soles of feet, ascending to legs and fingertips 	<p><u>Children:</u></p> <ul style="list-style-type: none"> • Around 1% overall • d4T—10% to 25% <p><u>Adults:</u></p> <ul style="list-style-type: none"> • d4T—up to 50% 	<ul style="list-style-type: none"> • 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. 	<p>Avoid use of d4T and ddl.</p> <p>Monitor for symptoms and signs of peripheral neuropathy.</p>	<p>Discontinue offending agent.</p> <p>Topical capsaicin 8% may be helpful.</p> <p>Consider referral to a neurologist.</p> <p>Data are insufficient to allow the Panel to recommend use of any of the following modalities: tricyclic antidepressants, gabapentin, pregabalin, mexiletine, Lamotrigine, and acupuncture or other complementary approaches</p>

^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; ddl = didanosine; INH = isoniazid; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor

Table 13I. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Rash and Hypersensitivity Reactions (Last updated April 27, 2017; last reviewed April 27, 2017) (page 1 of 4)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/Monitoring	Management
Rash	Any ARV can cause rash	<p><u>Onset:</u></p> <ul style="list-style-type: none"> • First few days to weeks after starting therapy <p><u>Presentation:</u></p> <ul style="list-style-type: none"> • Most rashes are mild-to-moderate, diffuse maculopapular eruptions. <p>Note: A rash can be the initial manifestation of systemic hypersensitivity (see Systemic HSR, SJS/TEN/EM Major)</p>	<p><u>Common (>10% Adults and/or Children):</u></p> <ul style="list-style-type: none"> • NVP, EFV, ETR, FPV, FTC <p><u>Less Common (5% to 10%):</u></p> <ul style="list-style-type: none"> • ABC, DRV, TPV, TDF <p><u>Unusual (2% to 4%):</u></p> <ul style="list-style-type: none"> • LPV/r, RAL, MVC, RPV 	<ul style="list-style-type: none"> • 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. 	<p><u>When Starting NVP or Restarting After Interruptions >14 Days:</u></p> <ul style="list-style-type: none"> • 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. 	<p><u>Mild-to-Moderate Maculopapular Rash Without Systemic or Mucosal Involvement:</u></p> <ul style="list-style-type: none"> • Most will resolve without intervention; ARVs can be continued while monitoring.^a • Antihistamines may provide some relief. <p><u>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):</u></p> <ul style="list-style-type: none"> • Manage as SJS/TEN/EM major (see below). <p><u>Rash in Patients Receiving NVP:</u></p> <ul style="list-style-type: none"> • Given elevated risk of HSR, measure hepatic transaminases. • If hepatic transaminases are elevated, NVP should be discontinued and not restarted (see HSR-NVP).
	ENF	<p><u>Onset:</u></p> <ul style="list-style-type: none"> • First few days to weeks after starting therapy <p><u>Presentation:</u></p> <ul style="list-style-type: none"> • Local injection site reactions with pain, erythema, induration, nodules and cysts, pruritus, ecchymosis. Often multiple reactions at the same time 	<p><u>Adults and Children:</u></p> <ul style="list-style-type: none"> • >90% 	Unknown	<ul style="list-style-type: none"> • Routinely assess patient for local reactions. • Rotate injection sites. • Massage area after injection. 	<ul style="list-style-type: none"> • Continue the agent as tolerated by the patient. • Ensure patient is injecting as per instructions. • Rotate injection sites.

Table 13I. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Rash and Hypersensitivity Reactions (Last updated April 27, 2017; last reviewed April 27, 2017) (page 2 of 4)

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)	<p><u>Onset:</u></p> <ul style="list-style-type: none"> • First few days to weeks after initiating therapy <p><u>Presentation:</u></p> <ul style="list-style-type: none"> • 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. 	<p><u>Infrequent:</u></p> <ul style="list-style-type: none"> • NVP (0.3%), EFV (0.1%), ETR (<0.1%) <p><u>Case Reports:</u></p> <ul style="list-style-type: none"> • FPV, ABC, DRV, ZDV, ddI, IDV, LPV/r, ATV, RAL 	<p><u>Adults:</u></p> <ul style="list-style-type: none"> • Female gender • Race/ethnicity (black, Asian, Hispanic) 	<p><u>When Starting NVP or Restarting After Interruptions >14 Days:</u></p> <ul style="list-style-type: none"> • Utilize once-daily lead-in dosing (see NVP section).^a • Counsel families to report symptoms as soon as they appear. 	<ul style="list-style-type: none"> • Discontinue all ARVs and other possible causative agents such as 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 with one NNRTI, many experts would avoid use of other NNRTIs.
DRESS	EFV, ETR, NVP, RAL, RPV, DRV	<p><u>Onset:</u></p> <ul style="list-style-type: none"> • 1–8 weeks <p><u>Presentation:</u></p> <ul style="list-style-type: none"> • Fever • Lymphadenopathy • Facial swelling • Morbilliform to polymorphous rash • Peripheral eosinophilia • Atypical circulating lymphocytes • Internal organ involvement (particularly liver and/or renal) 	Rare	Unknown	<ul style="list-style-type: none"> • Obtain CBC, AST, ALT and creatinine in patient presenting with suggestive symptoms. 	<ul style="list-style-type: none"> • Discontinue all ARVs and other possible causative agents such as TMP-SMX. • Role for steroids unclear; suggest consultation with specialist. • Supportive care for end-organ disease • Do not reintroduce the offending medication.

Table 13I. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Rash and Hypersensitivity Reactions (Last updated April 27, 2017; last reviewed April 27, 2017) (page 3 of 4)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/Monitoring	Management
<p>HSR</p> <p>With or without skin involvement and excluding SJS/TEN</p>	ABC	<p><u>Onset</u></p> <p><i>With First Use:</i></p> <ul style="list-style-type: none"> • Within first 6 weeks <p><i>With Reintroduction:</i></p> <ul style="list-style-type: none"> • Within hours <p><u>Presentation:</u></p> <ul style="list-style-type: none"> • Symptoms include high fever, diffuse skin rash, malaise, nausea, headache, myalgia, arthralgia, diarrhea, vomiting, abdominal pain, pharyngitis, respiratory symptoms (e.g., dyspnea). • Symptoms worsen to include hypotension and vascular collapse with continuation. With rechallenge, symptoms can mimic anaphylaxis. 	2.3% to 9% (varies by racial/ethnic group).	<ul style="list-style-type: none"> • HLA-B*5701 (HSR very uncommon in people who are HLA-B*5701-negative); also HLA-DR7, HLA-DQ3. • HSR risk is higher in those of white race compared to those of black or East Asian race. 	<ul style="list-style-type: none"> • 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. 	<ul style="list-style-type: none"> • 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 13I. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Rash and Hypersensitivity Reactions (Last updated April 27, 2017; last reviewed April 27, 2017) (page 4 of 4)

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	<p><u>Onset:</u></p> <ul style="list-style-type: none"> • Most frequent in the first few weeks of therapy but can occur through 18 weeks. <p><u>Presentation:</u></p> <ul style="list-style-type: none"> • Flu-like symptoms (including nausea, vomiting, myalgia, fatigue, fever, abdominal pain, jaundice) with or without skin rash that may progress to hepatic failure with encephalopathy. 	4% (2.5% to 11%)	<p><u>Adults:</u></p> <ul style="list-style-type: none"> • Treatment-naïve with higher CD4 count (>250 cells/mm³ in women; >400 cells/mm³ in men). • Female gender (risk is 3-fold higher in females compared with males). <p><u>Children:</u></p> <ul style="list-style-type: none"> • NVP hepatotoxicity and HSR are less common in pre-pubertal children than in adults. The PREDICT Study showed a 2.65 times higher risk of overall NVP toxicity (rash, hepatotoxicity, hypersensitivity) in children with CD4 ≥15% compared to children with CD4 <15%. 	<p><u>When Starting NVP or Restarting After Interruptions >14 Days:</u></p> <ul style="list-style-type: none"> • 2-week lead-in period with once-daily dosing then dose escalation to twice daily as recommended may reduce 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/mm³ and in men with CD4 counts >400 cells/mm³ unless benefits outweigh risks. • Do not use NVP in PEP. 	<ul style="list-style-type: none"> • Discontinue ARVs • Consider other causes for hepatitis and discontinue all hepatotoxic medications. • Provide supportive care as indicated and monitor 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.
	ENF, ETR	<p><u>Onset:</u></p> <ul style="list-style-type: none"> • Any time during therapy. <p><u>Presentation:</u></p> <ul style="list-style-type: none"> • Symptoms may include rash, constitutional findings, and sometimes organ dysfunction including hepatic failure. 	Rare	Unknown	<ul style="list-style-type: none"> • Evaluate for hypersensitivity if the patient is symptomatic. 	<ul style="list-style-type: none"> • Discontinue ARVs. • Rechallenge with ENF or ETR is not recommended.
	MVC	Rash preceding hepatotoxicity	Rare	Unknown	<ul style="list-style-type: none"> • Obtain AST and ALT in patients with rash or other symptoms of hypersensitivity. 	<ul style="list-style-type: none"> • Discontinue all ARVs • Rechallenge with MVC is not recommended.
	DTG	Rash with hepatic dysfunction	Rare	Unknown	<ul style="list-style-type: none"> • Obtain AST and ALT in patients with rash or other symptoms of hypersensitivity. 	<ul style="list-style-type: none"> • 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 consultation with an expert in HIV care should be obtained. **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 cell; ddI = didanosine; DRESS = drug rash with eosinophilia and systemic symptoms; DRV = darunavir; DTG = dolutegravir; EFV = efavirenz; EM = erythema multiforme; ENF = enfuvirtide; 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; TDF = tenofovir disoproxil fumarate; TEN = toxic epidermal necrolysis; TPV = tipranavir; ZDV = zidovudine

Table 14: 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 Regimens^a (page 1 of 2)

ARV Drug(s)	Age	Body Size Attained	Potential ARV Regimen Change	Comment ^b
NRTIs				
ABC Twice Daily	≥1 year	Any	ABC once daily	See Abacavir in Appendix A: Pediatric Antiretroviral Drug Information for full discussion.
ZDV or ddl (or d4T ^c)	≥1 year	N/A	ABC	Once-daily dosing (see Abacavir in Appendix A: Pediatric Antiretroviral Drug Information). Less long-term mitochondrial toxicity. TDF is a reasonable option for children unable to take ABC (HLA B5701 positive) who want to switch to a once-daily regimen.
	N/A	>35 kg	TAF or ABC	N/A
	Adolescence	Pubertal maturity (i.e., SMR IV or V)	TDF, TAF or ABC	Once-daily dosing. Less long-term mitochondrial toxicity. Coformulation with other ARV drugs can further reduce pill burden. TAF preferred over TDF for lower bone toxicity.
NNRTIs				
EFV	≥12 years	≥40 kg	ATV/r DRV/r DTG	Smaller pill (DTG), higher barrier to resistance given concern for adherence challenges developing in adolescents.
			RPV	DRV/r may be administered once daily in children aged ≥12 years without DRV resistance mutations.

Table 14: 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 Regimens^a (page 2 of 2)

ARV Drug(s)	Age	Body Size Attained	Potential ARV Regimen Change	Comment ^b
PIs				
LPV/r Twice Daily	≥1 year	≥3 kg	RAL ATV/r	Better palatability. Less adverse lipid effect. Lower pill burden. Once-daily dosing (ATV/r).
	≥3 years	N/A	ATV/r EFV RAL DTG (weighing ≥30 kg) EVG (weighing ≥25 kg)	Once-daily dosing (EFV and ATV/r). Better palatability. Less adverse lipid effect. See Efavirenz in Appendix A: Pediatric Antiretroviral Drug Information regarding concerns about dosing for children aged <3 years.
	≥12 years	≥40 kg	DRV/r ATV/r DTG RPV	Once-daily dosing possible. Lower pill burden.
Other				
Any Multi-Pill and/or Twice-Daily Regimen	Adolescence	For regimens with TDF: pubertal maturity (i.e., SMR IV or V)	Co-formulated: • TDF/FTC/EFV • TDF/FTC/EVG/COBI • TAF/FTC/EVG/COBI (weighing ≥35 kg) • TDF/FTC/RPV • TAF/FTC/RPV (weighing ≥35 kg) • ABC/3TC/DTG (weighing ≥40 kg) • TAF/FTC plus DTG	Once-daily dosing. Single pill. Alignment with adult regimens. TAF/FTC plus DTG may be more desirable because of small pill sizes even though it increases pill burden to 2 pills instead of 1. TAF-based regimens can be used with adolescents weighing ≥35 kg. Use ABC/3TC/DTG for adolescents weighing ≥40kg

^a This list is not exhaustive in that it does not necessarily list all potential options, but instead, shows examples of what kinds of changes can be made.

^b Comments relevant to the potential ARV change listed. Does not include all relevant information. Please refer to individual drug tables for full information.

^c Because of concerns about long-term adverse events, d4T should be replaced with a safer drug even before sustained virologic suppression is achieved (see [Stavudine](#) in [Appendix A: Pediatric Antiretroviral Drug Information](#)).

Key to Acronyms: 3TC = lamivudine; ABC = abacavir; ARV = antiretroviral; ATV/r = atazanavir/ritonavir; COBI = cobicistat; d4T = stavudine; ddl = didanosine; DRV/r = darunavir/ritonavir; DTG = dolutegravir; EFV = efavirenz; EVG = elvitegravir; FTC = emtricitabine; 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 (Tanner stage); TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; ZDV = zidovudine

Table 15. Discordance Among Virologic, Immunologic, and Clinical Responses

Differential Diagnosis of Poor Immunologic Response Despite Virologic Suppression
<p><u>Poor Immunologic Response Despite Virologic Suppression and Good Clinical Response:</u></p> <ul style="list-style-type: none">• Lab error (in CD4 or viral load result)• Misinterpretation of normal, age-related CD4 decline (i.e., immunologic response not actually poor)• Low pretreatment CD4 cell count or percentage• Adverse effects of use of ZDV or the combination of TDF and didanosine• Use of systemic corticosteroids or chemotherapeutic agents• Conditions that can cause low CD4 values, such as HCV, TB, malnutrition, Sjogren's syndrome, sarcoidosis, and syphilis <p><u>Poor Immunologic and Clinical Responses Despite Virologic Suppression:</u></p> <ul style="list-style-type: none">• Lab error• Falsely low viral load result for HIV strain/type 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 tuberculosis• Malignancy
Differential Diagnosis of Poor Clinical Response Despite Adequate Virologic and Immunologic Responses
<ul style="list-style-type: none">• IRIS• Previously unrecognized preexisting 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; HCV = hepatitis C virus; IRIS = immune reconstitution inflammatory syndrome; TB = tuberculosis; TDF = tenofovir disoproxil fumarate; ZDV = zidovudine

Table 16. 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	<ul style="list-style-type: none"> • 2 NRTIs plus PI • 2 NRTIs plus INSTI
2 NRTIs plus PI	<ul style="list-style-type: none"> • 2 NRTIs plus INSTI • 2 NRTIs plus different RTV-boosted PI • INSTI plus different RTV-boosted PI +/- NNRTI +/- NRTI(s)
2 NRTIs plus INSTI	<ul style="list-style-type: none"> • 2 NRTIs plus RTV-boosted PI • DTG (if not used in the prior regimen) + RTV-boosted PI +/- 1-2 NRTIs
Failed Regimen(s) That Included NRTI(s), NNRTI(s), and PI(s)	<ul style="list-style-type: none"> • INSTI + 2 NRTIs (if NRTIs are fully active) • INSTI + 2 NRTIs + RTV-boosted PI (if NRTIs are not fully active) • INSTI + RTV-boosted PI plus +/-ETR or RPV +/- NRTI(s) (if minimal NRTI activity) (consider adding T20 and/or MVC if additional active drug[s] needed)

^a ARV regimens should be chosen based on treatment history and drug-resistance testing to optimize ARV drug effectiveness. This is particularly important in selecting NRTI components of an NNRTI-based regimen where drug resistance to the NNRTI can occur rapidly if the virus is not sufficiently sensitive to the NRTIs. Regimens should contain at least 2, but preferably 3, fully active drugs for durable, 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 adjustment when devising a regimen for children with multi-class drug resistance.** Collaboration with a pediatric HIV specialist is especially important when choosing regimens for children with multi-class drug resistance. Regimens in this table are 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; T20 = enfuvirtide

Table 17. Target Trough Concentrations of Antiretroviral Drugs Relevant to Pediatric Populations^a

Drug	Plasma Trough Concentration (ng/mL) ± Standard Deviation
Atazanavir	2,000±1,000
Darunavir	2,200±1,100
Fosamprenavir	2,100
Lopinavir	5,500±4,000
Nelfinavir	700±400
Efavirenz	1,700±1,000
Nevirapine	4,500±1,900
Etravirine	300
Tipranavir	20,000–45,000
Raltegravir	65

^a Adapted from: Pretorius E, Klinker H, Rosenkranz B. The role of therapeutic drug monitoring in the management of patients with human immunodeficiency virus infection. *Ther Drug Monit.* 2011;33(3):265-274.