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 HIV-infected infants, children, and adolescents (through puberty) 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, ex officio 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 AIDS*info* website (http://aidsinfo.nih.gov).
Users of the Guidelines	Providers of care to HIV-infected infants, children, and adolescents in the United States
Developer	Panel on Antiretroviral Therapy and Medical Management of HIV-Infected Children—a working group of OARAC
Funding Source	Office of AIDS Research, NIH and HRSA
Evidence Collection	A standardized review of recent relevant literature related to each section of the guidelines is performed by a representative of the François-Xavier Bagnoud Center and provided to individual Panel section working groups. The recommendations are generally based on studies published in peer-reviewed journals. On some occasions, particularly when new information may affect patient safety, unpublished data presented at major conferences or prepared by the FDA and/or manufacturers as warnings to the public may be used as evidence to revise the guidelines.
Recommendation Grading	Described in Table 2.
Method of Synthesizing Data	Each section of the guidelines is assigned to a small group of Panel members with expertise in the area of interest. The members synthesize the available data and propose recommendations to the Panel. The Panel discusses 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.

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

Topic	Comment
Other Guidelines	These guidelines focus on HIV-infected infants, children, and adolescents in early puberty (SMR I-III). For more detailed discussion of issues of treatment for adolescents in late puberty (SMR IV-V), the Panel defers to the expertise offered by the Panel on Antiretroviral Guidelines for Adults and Adolescents. Separate guidelines outline the use of ART in HIV-infected pregnant women and interventions for prevention of perinatal transmission, ART for nonpregnant HIV-infected adults and postpubertal adolescents, and ARV prophylaxis for those who experience occupational or nonoccupational exposure to HIV. These guidelines are also available on the AIDS*info* website (http://www.aidsinfo.nih.gov).
Update Plan	The full Panel meets monthly by teleconference to review data that may warrant modification of the guidelines. Smaller working groups of Panel members hold additional teleconferences to review individual drug sections or other specific topics (e.g., What to Start). Updates may be prompted by new drug approvals (or new indications, formulations, or frequency of dosing), new significant safety or efficacy data, or other information that may have a significant impact on the clinical care of patients. In the event of significant new data that may affect patient safety, the Panel may issue a warning announcement and post accompanying recommendations on the AIDS*info* website until the guidelines can be updated with appropriate changes. All sections of the guidelines will be reviewed, with updates as appropriate, at least once yearly.
Public Comments	A 2-week public comment period follows release of the updated guidelines on the AIDS*info* website. The Panel reviews comments received to determine whether additional revisions to the guidelines are indicated. The public may also submit comments to the Panel at any time at contactus@aidsinfo.nih.gov.

Table 2. Rating Scheme for Recommendations

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

[a] Studies that include children or children and adolescents, but not studies limited to postpubertal 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	√		√				√	
Urinalysis	√		√				√	
Hepatitis B Screening[6,7]		√						√

[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 45 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 tenofovir disoproxil fumarate, 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 = combination 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 (page 1 of 2)

Mild HIV-Related Symptoms
Children with two or more of the conditions listed but none of the conditions listed in Moderate Symptoms category • Lymphadenopathy (≥0.5 cm at more than 2 sites; bilateral at 1 site) • Hepatomegaly • Splenomegaly • Dermatitis • Parotitis • Recurrent or persistent upper respiratory tract infection, sinusitis, or otitis media
Moderate HIV-Related Symptoms
• Anemia (hemoglobin <8 g/dL [<80 g/L]), neutropenia (white blood cell count <1,000/μL [<1.0 × 109/L]), and/or thrombocytopenia (platelet count <100 × 103/μL [<100 × 109/L]) persisting for ≥30 days • Bacterial meningitis, pneumonia, or sepsis (single episode) • Candidiasis, oropharyngeal (thrush), persisting (>2 months) in children older than age 6 months • Cardiomyopathy • Cytomegalovirus infection, with onset before 1 month • Diarrhea, recurrent or chronic • Hepatitis • Herpes simplex virus (HSV) stomatitis, recurrent (>2 episodes within 1 year) • HSV bronchitis, pneumonitis, or esophagitis with onset before 1 month • Herpes zoster (shingles) involving at least 2 distinct episodes or more than 1 dermatome • Leiomyosarcoma • Lymphoid interstitial pneumonia or pulmonary lymphoid hyperplasia complex • Nephropathy • Nocardiosis • Persistent fever (lasting >1 month) • Toxoplasmosis, onset before 1 month • Varicella, disseminated (complicated chickenpox)

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

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

[a] Only among children aged <6 years.

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

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

- Centers for Disease Control and Prevention. 1994 Revised classification system for human immunodeficiency virus infection in children less than 13 years of age. *MMWR*. 1994;43(No. RR-12).
- Centers for Disease Control and Prevention. 1993 Revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. *MMWR*. 1992;41(No. RR-17).

Modified from:

- Centers for Disease Control and Prevention. 1994 revised classification system for human immunodeficiency virus infection in children less than 13 years of age. *MMWR*. 1994;43(No. RR-12).
- Centers for Disease Control and Prevention: Revised Surveillance Case Definition for HIV Infection—United States, 2014. *MMWR*. 2014;63(No. RR-3):1-10.

Table 7. Antiretroviral Regimens Recommended for Initial Therapy for HIV Infection in Children
(page 1 of 2)

An ART regimen in treatment-naive children generally contains one NNRTI or one PI boosted with ritonavir or one INSTI **plus** a two-NRTI backbone. 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	
Children aged ≥14 Days to <3 Years[a]	Two NRTIs **plus** LPV/r
Children Aged ≥2 Years to <3 Years	Two NRTIs plus LPV/r
	Two NRTIs plus RAL[b]

Table 7. Antiretroviral Regimens Recommended for Initial Therapy for HIV Infection in Children
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Preferred Regimens, continued	
Children Aged ≥3 Years to <12 Years	Two NRTIs **plus** ATV/r
	Two NRTIs **plus** twice daily DRV/r
	Two NRTIs **plus** EFV[c]
	Two NRTIs **plus** LPV/r
	Two NRTIs **plus** RAL[b]
Adolescents Aged ≥12 Years and Not Sexually Mature (SMR I–III)	Two NRTIs **plus** ATV/r
	Two NRTIs **plus** DTG[d]
	Two NRTIs **plus** once daily DRV/r[e]
	Two NRTIs **plus** EVG/c[f]
Adolescents Aged ≥12 Years and Sexually Mature (SMR IV or V)	Refer to Guidelines for the Use of Antiretroviral Agents in HIV-1 Infected Adults and Adolescents
Alternative Regimens	
Children Aged >14 Days to <3 Years	Two NRTIs **plus** NVP[g]
Children Aged ≥4 Weeks and <2 Years and Weighing ≥3 kg	Two NRTIs **plus** RAL[b]
Children Aged ≥3 Months to <3 Years and Weighing ≥10 kg	Two NRTIs **plus** ATV/r
Adolescents Aged ≥12 Years and Not Sexually Mature (SMR I–III)	Two NRTIs **plus** EFV[c]
	Two NRTIs **plus** RAL[b]
	Two NRTIs **plus** RPV[h]
Preferred 2-NRTI Backbone Options for Use in Combination with Additional Drugs	
Children, Birth to 3 Months	ZDV **plus** (3TC **or** FTC)
Children Aged ≥3 Months and <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/FTC
Adolescents Aged ≥12 Years and Sexually Mature (SMR IV or V)	Refer to Guidelines for the Use of Antiretroviral Agents in HIV-1 Infected Adults and Adolescents
Alternative 2-NRTI Backbone Options for Use in Combination with Additional Drugs	
Children Aged ≥2 Weeks	ddI **plus** (3TC **or** FTC)
	ZDV **plus** ddI
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	TDF **plus** (3TC **or** FTC)

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

[b] 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.

[c] EFV 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. Unless adequate contraception can be ensured, EFV-based therapy is not recommended for adolescent females who are sexually active and may become pregnant.

[d] DTG is recommended only for those adolescents aged ≥12 years and weighing ≥40 kg.

[e] DRV once daily should not be used in children aged <12 years and if any one of the following resistance-associated substitutions are present: V11I, V32I, L33F, I47V, I50V, I54L, I54M, T74P, L76V, I84V, and L89V.

[f] EVG is currently recommended only in fixed-dose combination tablets. Tablets containing elvitegravir/cobicistat/emtricitabine/TAF are recommended as Preferred for children aged ≥12 years and weighing ≥35 kg. Tablets containing elvitegravir/cobicistat/emtricitabine/TDF are recommended only for adolescents aged ≥12 years, weighing ≥35 kg, and in SMR IV or V.

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

[h] 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; ddI = didanosine; DRV = darunavir; DRV/r = darunavir/ritonavir; DTG = dolutegravir; EFV = efavirenz; EVG = elvitegravir; EVG/c = elvitegravir/cobicistat; 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; RTV = ritonavir; 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 3)

ARV Class	ARV Agent(s)	Advantages	Disadvantages
INSTIs In Alphabetical Order		Integrase Inhibitor Class Advantages: • Susceptibility of HIV to a new class of ARVs • Few drug-drug interactions • Well tolerated	Integrase Inhibitor Class Disadvantages: • Limited data on pediatric dosing or safety
	DTG	• Once-daily administration • Can give with food	• Drug interactions with EFV, FPV/r, TPV/r, and rifampin necessitating twice-daily dosing
	EVG	• Once-daily administration • Available as a tablet and 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)	• COBI has the potential for multiple drug interactions because of metabolism via hepatic enzymes (e.g., CYP3A4) • TAF inhibits tubular secretion of creatinine and may result in increased serum creatinine but with normal glomerular clearance
	RAL	• Can give with food • Available in tablet, chewable tablet and powder formulations	• Potential for rare systemic allergic reaction or hepatitis
NNRTIs In Alphabetical Order		NNRTI Class Advantages: • Long half-life • Less dyslipidemia and fat maldistribution than PIs • PI-sparing • Lower pill burden than PIs for children taking solid formulation; easier to use and adhere to than PI-based regimens	NNRTI Class Disadvantages: • Single mutation can confer resistance, with cross-resistance between EFV and NVP. • Rare but serious and potentially life-threatening cases of skin rash, including SJS, and hepatic toxicity with all NNRTIs (but highest with NVP) • Potential for multiple drug interactions due to metabolism via hepatic enzymes (e.g., CYP3A4)
	EFV	• Once-daily administration • Potent ARV activity • Can give with food (but avoid high-fat meals) • Capsules can be opened and added to food	• Neuropsychiatric AEs (bedtime dosing recommended to reduce CNS effects) • Rash (generally mild) • No commercially available liquid • Limited data on dosing for children aged <3 year • No data on dosing for children aged <3 months • Use with caution in adolescent females of childbearing age
	NVP	• Liquid formulation available • Dosing information for young infants available • Can give with food • Extended-release formulation is available that allows for once-daily dosing in older children	• Reduced virologic efficacy in young infants, regardless of exposure to NVP as part of a peripartum preventive regimen • Higher incidence of rash/HSR than other NNRTIs • Higher rates of serious hepatic toxicity than EFV • Decreased virologic response compared with EFV • Twice dosing necessary in children with BSA <0.58 m^2
	RPV	• Once-daily dosing • Available in a one-pill daily fixed drug combination	• Should not use in patients with HIV viral load >100,000 copies/mL • Low barrier for resistance

Table 8. Advantages and Disadvantages of Antiretroviral Components Recommended for Initial Therapy in Children[a] (page 2 of 3)

ARV Class	ARV Agent(s)	Advantages	Disadvantages
PIs In Alphabetical Order		PI Class Advantages: • 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 two steps of viral replication (viral reverse transcriptase and protease enzymes)	PI Class Disadvantages: • Metabolic complications including dyslipidemia, fat maldistribution, insulin resistance • Potential for multiple drug interactions because of metabolism via hepatic enzymes (e.g., CYP3A4) • Higher pill burden than NRTI- or NNRTI-based regimens for patients taking solid formulations • Poor palatability of liquid preparations, which may affect adherence to treatment regimen • Most PIs require ritonavir boosting resulting in associated drug interactions
	ATV/r	• 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)	• No liquid formulation • Food effect (should be administered with food) • Indirect hyperbilirubinemia is common but asymptomatic • Must be used with caution in patients with pre-existing conduction system defects (can prolong PR interval of ECG) • RTV component associated with large number of drug interactions
	DRV/r	• Can be used once daily in children aged ≥12 years • Liquid formulation available	• Pediatric pill burden high with current tablet dose formulations • Food effect (should be given with food) • Must be given with RTV boosting to achieve adequate plasma concentrations • Contains sulfa moiety. The potential for cross sensitivity between DRV and other drugs in sulfonamide class is unknown • 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	• LPV only available coformulated with RTV in liquid and tablet formulations • Tablets can be given without regard to food but may be better tolerated when taken with meal or snack	• Poor palatability of liquid formulation (bitter taste), although palatability of combination 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 3)

ARV Class	ARV Agent(s)	Advantages	Disadvantages
Dual-NRTI Backbones In Alphabetical Order	ABC **plus** (3TC **or** FTC)	• Palatable liquid formulations • Can give with food • ABC and 3TC are coformulated as a single pill for older/larger patients; ABC, 3TC are also coformulated with DTG for use in adults	• Risk of ABC HSR; perform HLA-B*5701 screening before initiation of ABC treatment
	ddI **plus** (3TC **or** FTC)	• Delayed-release capsules of ddI 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	• Food effect (ddI is recommended to be taken 1 hour before or 2 hours after food). Some experts give ddI without regard to food in infants or when adherence is an issue (ddI can be co-administered with FTC or 3TC) • Limited pediatric experience using delayed-release ddI capsules in younger children • Pancreatitis, lactic acidosis, neurotoxicity with ddI
	TAF **plus** FTC	• Once-daily dosing • Less tenofovir-associated renal and bone toxicity with TAF compared to TDF in adults	• Only available as a fixed-dose combination tablet consisting of EVG, COBI, FTC, and TAF; RPV, FTC, and TAF; or TAF and FTC for adolescents ≥12 years
	TDF **plus** (3TC **or** FTC) for adolescents, SMR IV or V	• Once-daily dosing for TDF • Resistance is slow to develop • Less mitochondrial toxicity than other NRTIs • Can give with food • TDF and FTC are co-formulated as single pill for older/larger patients • Available as reduced-strength tablets and oral powder for use in younger children	• Limited pediatric experience • Potential bone and renal toxicity, toxicity may be less in postpubertal children • Appropriate dosing is complicated by numerous drug-drug interactions with other ARV agents including ddI, LPV/r, ATV, and TPV
	ZDV **plus** (3TC **or** FTC)	• Extensive pediatric experience • ZDV and 3TC are coformulated as single pill for older/larger patients • Palatable liquid formulations • Can give with food • FTC is available as a palatable liquid formulation administered once daily	• Bone marrow suppression with ZDV • Lipoatrophy with ZDV
	ZDV **plus** ABC	• Palatable liquid formulations • Can give with food	• Risk of ABC HSR; perform HLA-B*5701 screening before initiation of ABC treatment • Bone marrow suppression and lipoatrophy with ZDV
	ZDV **plus** ddI	• Extensive pediatric experience • Delayed-release capsules of ddI may allow SMR dosing of ddI in older children able to swallow pills and who can receive adult doses	• Bone marrow suppression and lipoatrophy with ZDV • Pancreatitis, neurotoxicity with ddI • ddI liquid formulation is less palatable than 3TC or FTC liquid formulation • Food effect (ddI is recommended to be taken 1 hour before or 2 hours after food). Some experts give ddI without regard to food in infants or when adherence is an issue

[a] See Appendix A: Pediatric Antiretroviral Drug Information for more information.

Key to Acronyms: 3TC = lamivudine; ABC = abacavir; ARV = antiretroviral; ATV/r = atazanavir/ritonavir; BSA = body surface area; CNS = central nervous system; COBI = cobicistat; DRV/r = darunavir/ritonavir; ddI = didanosine; DTG = dolutegravir; ECG = electrocardiogram; EFV = efavirenz; EVG=elvitegravir; 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; ZDV = zidovudine

Table 9. Antiretroviral Regimens or Components Not Recommended for Initial Treatment of HIV Infection in Children (page 1 of 2)

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 ddI**	Insufficient data to recommend
Dual NRTI combination of **ABC plus TDF**	Insufficient data to recommend

Table 9. Antiretroviral Regimens or Components Not Recommended for Initial Treatment of HIV Infection in Children (page 2 of 2)

Regimen or ARV Component	Rationale for Being Not Recommended
Regimens containing **d4T**	Increased toxicities
Dual NRTI combination of **TDF plus ddI**	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 three drug classes	Insufficient data to recommend
Full-dose **RTV** or use of **RTV** as the sole PI	GI intolerance Metabolic toxicity
Regimens containing three NRTIs and an 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; ddI = 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; 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 Never Recommended for Children		
Regimen	**Rationale**	**Exceptions**
One ARV drug alone (monotherapy)	• 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	• HIV-exposed infants (with negative viral testing) during 6-week period of prophylaxis to prevent perinatal transmission of HIV
Two NRTIs Alone	• Rapid development of resistance • Inferior antiviral activity compared with combination including ≥3 ARV drugs	• Not recommended for initial therapy • For patients currently on 2 NRTIs alone who achieve virologic goals, some clinicians may opt to continue this treatment.
TDF plus ABC plus (3TC or FTC) as a Triple-NRTI Regimen	• High rate of early viral failure when this triple-NRTI regimen was used as initial therapy in treatment-naive adults.	• No exceptions
TDF plus ddI plus (3TC or FTC) as a Triple-NRTI Regimen	• High rate of early viral failure when this triple-NRTI regimen was used as initial therapy in treatment-naive adults.	• No exceptions
ARV Components Never Recommended as Part of an ARV Regimen for Children		
Regimen	**Rationale**	**Exceptions**
ATV plus IDV	• Potential additive hyperbilirubinemia	• No exceptions
Dual-NNRTI Combinations	• Enhanced toxicity	• No exceptions
Dual-NRTI Combinations: **• 3TC plus FTC**	• Similar resistance profile and no additive benefit	• No exceptions
• d4T plus ZDV	• Antagonistic effect on HIV	• No exceptions
EFV for Sexually Active Adolescent Girls of Childbearing Potential When Reliable Contraception Cannot Be Ensured	• Teratogenicity in primates (see General Principles Regarding Use of Antiretroviral Drugs during Pregnancy Teratogenicity	• When no other ARV option is available and potential benefits outweigh risks
NVP as Initial Therapy in Adolescent Girls with CD4 Count >250 cells/mm³ or Adolescent Boys with CD4 Count >400 cells/mm³	• Increased incidence of symptomatic (including serious and potentially fatal) hepatic events in these patient groups	• Only if benefit clearly outweighs risk
Unboosted SQV, DRV, or TPV	• Poor oral bioavailability • Inferior virologic activity compared with other PIs	• No exceptions

Key to 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. Strategies to Improve Adherence to Antiretroviral Medications

Initial Intervention Strategies
• Establish trust and identify mutually acceptable goals for care.
• Obtain explicit agreement on the need for treatment and adherence.
• Identify depression, low self-esteem, substance abuse, or other mental health issues for 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 1) the relationship between partial adherence and resistance; and 2) 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.
• 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.
Medication Strategies
• 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.
Follow-Up Intervention Strategies
• Have more than one member of the multidisciplinary team monitor adherence at each visit and in between visits by telephone, email, text, and social media, as needed.
• Provide ongoing support, encouragement, and understanding of the difficulties associated with maintaining adherence to daily medication regimens.
• Use patient education aids including pictures, calendars, and stickers.
• Encourage use of pill boxes, reminders, alarms, pagers, and timers.
• Provide follow-up clinic visits, telephone calls, and text messages to support and assess adherence.
• Provide access to support groups, peer groups, or one-on-one counseling for caregivers and patients, especially for those with known depression or drug use issues that are known to decrease adherence.
• Provide pharmacist-based adherence support, such as medication education and counseling, 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 12a. Antiretroviral-Therapy-Associated Adverse Effects and Management Recommendations—Central Nervous System Toxicity (Last updated March 1, 2016; last reviewed March 1, 2016) (page 1 of 3)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
Global CNS Depression	LPV/r oral solution (contains both ethanol and propylene glycol as excipients)	Onset: • 1–6 days after starting LPV/r Presentation *Neonates/Preterm Infants:* • Global CNS depression (e.g., abnormal EEG, altered state of consciousness, somnolence) • Non-CNS-associated toxicity may include cardiac toxicity and respiratory complications.	Exact frequency of ethanol and propylene glycol-associated toxicity unknown in neonates receiving LPV/r oral solution.	Prematurity Low birth weight Age <14 days (whether premature or term)	Avoid use of LPV/r until a postmenstrual age of 42 weeks and a postnatal age ≥14 days.	Discontinue LPV/r; symptoms should resolve in 1–5 days. If needed, reintroduction of LPV/r can be considered once outside the vulnerable period (i.e., postmenstrual age of 42 weeks and a postnatal age ≥14 days).
Neuropsychiatric Symptoms and Other CNS Manifestations	EFV	Onset: • 1–2 days after initiating treatment • 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. Presentation (May Include One or More of the Following) *Neuropsychiatric Symptoms:* • Abnormal dreams • Psychosis • Suicidal ideation or attempted/completed suicide • Seizures (including absence seizures) or decreased seizure threshold	Variable, depending on age, symptom, assessment method Children: • 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 two of the children the seizures had alternative causes. Adults: • 30% incidence for any CNS manifestations of any severity. • 6% incidence for EFV-related severe CNS manifestations including suicidality.	Insomnia associated with elevated EFV trough concentration ≥4 mcg/mL Presence of CYP450 polymorphisms that decrease EFV metabolism (CYP2B6 516 TT genotype) Prior history of psychiatric illness or use of psychoactive drugs	Administer EFV on an empty stomach, preferably at bedtime. Use with caution in the presence of psychiatric illness including depression or suicidal thoughts or with concomitant use of psychoactive drugs. 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).	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). 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.

Table 12a. Antiretroviral-Therapy-Associated Adverse Effects and Management Recommendations—Central Nervous System (CNS) Toxicity (Last updated March 1, 2016; last reviewed March 1, 2016) (page 2 of 3)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
Neuropsychiatric Symptoms and Other CNS Manifestations, continued	EFV, continued	*Other CNS Manifestations:* • Dizziness • Somnolence • Insomnia or poor sleep quality • Impaired concentration **Note:** Some CNS side effects (e.g., impaired concentration, abnormal dreams, or sleep disturbances) may be more difficult to assess in children.	However, evidence is conflicting about whether EFV use increases the incidence of suicidality.			
	RPV	Presentation *Neuropsychiatric Symptoms:* • Depressive disorders • Suicidal ideation • Abnormal dreams/ nightmare *Other CNS Manifestations:* • Headache • Dizziness • Insomnia	In Adults: • CNS/neuropsychiatric 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. In Children: • 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.	Prior history of neuropsychiatric illness	Monitor carefully for depressive disorders and other CNS symptoms.	Consider drug substitution in case of severe symptoms.
	RAL	Presentation: • Increased psychomotor activity • Headaches • Insomnia • Depression	Children: • Increased psychomotor activity reported in one child. Adults: • Headache • Insomnia (<5% in adult trials)	Elevated RAL concentrations Co-treatment with TDF or PPI Prior history of insomnia or depression	Prescreen for psychiatric symptoms. Monitor carefully for CNS symptoms. Use with caution in the presence of drugs that increase RAL concentration.	Consider drug substitution (RAL or co-administered drug) in case of severe insomnia or other neuropsychiatric symptoms.

Table 12a. Antiretroviral-Therapy-Associated Adverse Effects and Management Recommendations—Central Nervous System (CNS) Toxicity (Last updated March 1, 2016; last reviewed March 1, 2016) (page 3 of 3)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
	DTG	Onset: • 7–30 days after initiating drug Presentation *Neuropsychiatric Symptoms:* • Depression or exacerbation of preexisting depression • Anxiety • Suicidal ideation attempt, behavior, or completion *Other CNS Manifestations (Generally Mild):* • Insomnia • Dizziness • Headache	Adults • 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% patients experienced more severe symptoms.	Pre-existing depression or other psychiatric illness	Use with caution in the presence of psychiatric illness especially depression	For severe neuropsychiatric symptoms, consider discontinuation of DTG if suitable alternative exists. Discontinuation resulted in resolution of neuropsychiatric symptom in 3 out of 4 patients (in the 4th patient, symptoms resolved slowly despite DTG continuation). For mild symptoms, continue DTG and counsel patient that symptoms will likely resolve with time.
Intracranial Hemorrhage	TPV	Onset: • 7–513 days after starting TPV	Children: • No cases of ICH reported in children. Adults: • In premarket approval data in adults, 0.23/100 py or 0.04–0.22/100 py in a retrospective review of 2 large patient databases.	Unknown; prior history of bleeding disorder or risk factors for bleeding 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.
Cerebellar Ataxia	RAL	Onset: • As early as 3 days after starting RAL Presentation: • Tremor • Dysmetria • Ataxia	Two cases reported in adults during post-marketing period.	Unknown; a speculated mechanism may include recent treatment with ATV with residual UGT1A1 enzyme inhibition and increased RAL serum concentration.	Use with caution with ATV or other drugs that cause strong inhibition of UGT1A1 enzyme.	Consider drug discontinuation. RAL reintroduction can be considered if predisposing factor (e.g., drug-drug interaction) identified and removed.

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

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Table 12b. Antiretroviral-Therapy-Associated Adverse Effects and Management Recommendations—Dyslipidemia

(Last updated March 1, 2016; last reviewed March 1, 2016) (page 1 of 2)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
Dyslipidemia	PIs: • All PIs, especially RTV-boosted PIs; lower incidence reported with DRV/r and ATV with or without RTV. NRTIs: • Especially d4T NNRTIs: • EFV > NVP, RPV, and ETR	Onset: • As early as 2 weeks to months after beginning therapy Presentation *PIs:* • ↑LDL-C, TC, and TG *NNRTIs:* • ↑LDL-C, TC, and HDL-C *NRTIs:* • ↑LDL-C, TC, and TG	Reported frequency varies with specific ARV regimen, duration of ART and specific laboratory parameters used to diagnose lipid abnormalities. 10% to 20% in young children receiving LPV/RTV 40% to 75% of older children and adolescents with prolonged ART history will have lipid abnormalities. In studies of treatment naive adults, 38% and 32% receiving EVG/COBI/FTC/TAF developed abnormal fasting TC and LDL-C (respectively) after 48 weeks compared with 21% and 20% receiving EVG/COBI/FTC/TDF, difference mainly attributable to TAF In 48 adolescents treated with EVG/COBI/FTC/TAF median change from baseline to	Advanced-stage HIV disease High-fat, high-cholesterol diet Lack of exercise Obesity Hypertension Smoking Family history of dyslipidemia or premature CVD Metabolic syndrome Fat maldistribution	Prevention: • Low-fat diet • Exercise • Smoking-prevention counseling Monitoring[a] *Adolescents and Adults:* • Monitor 12-hour FLP, which includes TC, HDL-C, non-HDL-C, LDL-C, and TG, every 6–12 months. Obtain FLPs twice (>2 weeks but ≤3 months apart, average results) before initiating or changing lipid-lowering therapy. *Children (Aged ≥2 Years) without Lipid Abnormalities or Additional Risk Factors:* • Obtain non-fasting screening lipid profiles before initiating or changing therapy and then, if levels are stable, every 6–12 months. If TG or LDL-C is elevated, obtain fasting blood tests. *Children with Lipid Abnormalities and/or Additional Risk Factors:* • Obtain 12-hour FLP before initiating or changing therapy and every 6 months thereafter (more often if indicated). *Children Receiving Lipid-Lowering Therapy with Statins or Fibrates:* • Obtain 12-hour FLP, LFTs, and CK at 4 and 8 weeks, and 3	Assessment of additional CVD risk factors should be done in all patients. HIV-infected patients are considered to be at moderate risk of CVD.[b] 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 trans fat, physical activity, smoking cessation) for an adequate trial period (3–6 months). Consider consultation with dietician. If receiving d4T, it should be discontinued. If receiving PI-based ART, consider switching to a new PI-sparing ART regimen or PI-based regimen containing boosted ATV or DRV, which are less likely to cause lipid abnormalities. Consider lipid-lowering therapy in consultation with a lipid specialist if ≥6-month trial of lifestyle modification fails. Some experts suggest treatment in children receiving ARV drugs at cut points recommended by NHLBI cardiovascular risk reduction guidelines for children aged ≥10 years: LDL-C ≥190 mg/dL, regardless of additional risk factors; LDL-C ≥160 mg/dL or LDL-C ≥130 mg/dL based on presence of additional risk factors and risk conditions.[b] The minimal goal of therapy should be to achieve and maintain a LDL-C value below 130 mg/dL.

Table 12b. Antiretroviral-Therapy-Associated Adverse Effects and Management Recommendations—Dyslipidemia

(Last updated March 1, 2016; last reviewed March 1, 2016) (page 2 of 2)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
			weeks 24 and 36 were 26 mg/dl and 36 mg/dl, respectively for fasting TC, and 10 mg/dl and 17 mg/dl, respectively for direct LDL-C.		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.	Initiate Drug Therapy Promptly in Patients with Fasting TG ≥500 mg/dL: Statins such as pravastatin, atorvastatin, or rosuvastatin.[c] Ezetimibe can be considered in addition to statins.[d] Statin-related toxicities include liver enzyme elevation and myopathy, and risk may be increased by drug interactions with ART, particularly PIs.[c] Risks must be weighed against potential benefits. Fibrates (gemfibrozil and fenofibrate) and N-3 PUFAs derived from fish oils may be used as alternative agents for adults with ↑TG but are not approved for use in children. The long-term risks of lipid abnormalities in children receiving ART are unclear. However, persistent dyslipidemia in children may lead to premature CVD.

[a] Given the burden of collecting fasting blood samples, some practitioners routinely measure cholesterol and triglycerides from 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 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

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Table 12c. Antiretroviral-Therapy-Associated Adverse Effects and Management Recommendations—Gastrointestinal Effects (Last updated March 1, 2016; last reviewed March 1, 2016)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
Nausea/ Vomiting	Principally ZDV and PIs (e.g., LPV/r, RTV), but can occur with all ARVs and COBI	Onset: • Early Presentation: • Nausea, emesis—may be associated with anorexia and/or abdominal pain.	Varies with ARV agent; 10% to 30% in some series	Unknown	Instruct patient to take PIs with food. Generally improves with time; monitor for weight loss, ARV adherence.	Reassure patient/caretaker that nausea and vomiting will likely decrease over time. Provide supportive care, including instruction on dietary modification. Although antiemetics are not generally indicated, they may be useful in extreme or persistent cases.
Diarrhea	PIs (particularly NFV, LPV/r, FPV/r), buffered ddI, INSTI (mild)	Onset: • Early Presentation: • Generally soft, more frequent stools	Varies with ARV agent; 10% to 30% in some series	Unknown	Generally improves with time (usually over 6–8 weeks); monitor for weight loss, dehydration.	Exclude infectious causes of diarrhea. Although data in children on treatment of ARV-associated diarrhea are lacking, dietary modification, use of calcium carbonate (should not be used with DTG), bulk-forming agents (psyllium), or antimotility agents (loperamide) may be helpful. While there are few published data on its use, crofelemer is FDA-approved for treatment of ART-associated diarrhea in adults but **not** in children.
Pancreatitis	ddI, d4T (especially concurrently or with TDF), boosted PIs Reported, albeit rarely, with most ARVs.	Onset: • Any time, usually after months of therapy Presentation: • Emesis, abdominal pain, elevated amylase and lipase (asymptomatic hyperamylasemia or elevated lipase do not in and of themselves indicate pancreatitis).	<2% in recent series Frequency was higher in the past with higher dosing of ddI.	Concomitant treatment with other medications associated with pancreatitis (e.g., TMP-SMX, pentamidine, ribavirin) Hypertriglyceridemia Advanced disease Previous episode of pancreatitis	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

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Table 12d. Antiretroviral-Therapy-Associated Adverse Effects and Management Recommendations—Hematologic Effects (Last updated March 1, 2016; last reviewed March 1, 2016) (page 1 of 2)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
Anemia[a]	Principally ZDV	Onset: • Variable, weeks to months Presentation *Most Commonly:* • Asymptomatic or mild fatigue • Pallor • Tachypnea *Rarely:* • Congestive heart failure	HIV-Exposed Newborns: • Severe anemia is uncommon, but may be seen coincident with physiologic Hgb nadir. HIV-Infected Children on ARVs: • 2–3 times more common with ZDV-containing regimens; less frequent with currently recommended dosing of ZDV	HIV-Exposed Newborns: • Premature birth • *In utero* exposure to ARVs • Advanced maternal HIV • Neonatal blood loss • Combination ARV prophylaxis, particularly with ZDV plus 3TC HIV-Infected Children on ARVs: • Underlying hemoglobinopathy (e.g., sickle cell disease, G6PD deficiency) • Myelosuppressive drugs (e.g., TMP-SMX, rifabutin) • Iron deficiency • Advanced or poorly controlled HIV disease • Malnutrition	HIV-Exposed Newborns: • 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). HIV-Infected Children on ARVs: • Avoid ZDV in children with moderate to severe anemia when alternative agents are available. • Obtain CBC as part of routine care.	HIV-Exposed Newborns: • Rarely require intervention unless Hgb is <7.0 g/dL or anemia is associated with symptoms. • Consider discontinuing ZDV if 4 weeks or more of a 6-week ZDV prophylaxis regimen are already completed (see the Perinatal Guidelines[b]). HIV-Infected Children on ARVs: • Discontinue non-ARV, marrow-toxic drugs, if feasible. • Treat coexisting iron deficiency, OIs, malignancies. • For persistent severe anemia thought to be associated with ARVs, change to a non-ZDV-containing regimen; consider a trial of erythropoietin if essential to continue ZDV.
Macrocytosis	Principally ZDV; also d4T	Onset: • Within days to weeks of starting therapy • MCV often >100 fL Presentation: • 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.	None required unless associated with anemia

Table 12d. Antiretroviral-Therapy-Associated Adverse Effects and Management Recommendations—Hematologic Effects (Last updated March 1, 2016; last reviewed March 1, 2016) (page 2 of 2)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
Neutropenia[a]	Principally ZDV	Onset: • Variable Presentation: • Most commonly asymptomatic. Complications appear to be less than with neutropenias associated with cancer chemotherapy.	HIV-Exposed Newborns: • Rare HIV-Infected Children on ARVs: • 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	HIV-Exposed Newborns: • *In utero* exposure to ARVs • Combination ARV prophylaxis, particularly with ZDV plus 3TC HIV-Infected Children on ARVs: • Advanced or poorly controlled HIV infection • Myelosuppressive drugs (e.g., TMP-SMX, ganciclovir, hydroxyurea, rifabutin)	HIV-Infected Children on ARVs: • Obtain CBC as part of routine care.	HIV-Exposed Newborns: • No established threshold for intervention; some experts would consider using an alternative NRTI for prophylaxis if ANC <500 cells/mm^3, or discontinue ARV prophylaxis entirely if ≥4 weeks of 6-week ZDV prophylaxis have been completed (see the Perinatal Guidelines[b]). HIV-Infected Children on ARVs: • Discontinue non-ARV marrow-toxic drugs, if feasible. • Treat coexisting OIs and malignancies. • For persistent severe neutropenia thought to be associated with ARVs, change to a non-ZDV-containing regimen. Consider a trial of G-CSF if essential to continue ZDV.

[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; G-CSF = granulocyte colony-stimulating factor; Hgb = hemoglobin; MCV = mean cell volume; NRTI = nucleoside reverse transcriptase inhibitor; OI = opportunistic infection; TMP-SMX = trimethoprim-sulfamethoxazole; ZDV = zidovudine

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Table 12e. Antiretroviral-Therapy-Associated Adverse Effects and Management Recommendations—Hepatic Events

(Last updated March 1, 2016; last reviewed March 1, 2016) (page 1 of 2)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
Hepatic Toxicity Elevated AST, ALT, clinical hepatitis	All ARVs may be associated with hepatitis. NVP and TPV are of particular concern. NVP, EFV, ABC, RAL, and MVC have been associated with hypersensitivity reactions. NRTIs (especially ZDV, ddI, and d4T) are associated with lactic acidosis and hepatic steatosis.	Onset: • Hepatitis generally occurs within the first few months of therapy, but can occur later. • Steatosis presents after months to years of therapy. • HBV-coinfected patients may develop severe hepatic flare with the initiation, withdrawal, or development of resistance to 3TC, FTC, or TDF (especially in patients receiving only one anti-HBV agent). • Hepatitis may also represent IRIS early in therapy, especially in HBV- and HCV-infected patients. Presentation: • Asymptomatic elevation of AST and ALT • Symptomatic hepatitis with nausea, fatigue, and jaundice • Hepatitis may be component of hypersensitivity reaction with rash, lactic acidosis, and hepatic steatosis.	Uncommon in children Frequency varies with different agents and drug combinations.	HBV or HCV coinfection Elevated baseline ALT and AST Other hepatotoxic medications (including herbal preparations such as St. John's wort [*Hypericum perforatum*], Chaparral [*Larrea tridentate*], Germander [*Teucrium chamaedrys*]) Alcohol use Underlying liver disease Pregnancy For NVP-Associated Hepatic Events in Adults: • Female with pre-NVP CD4 count >250 cells/mm^3 • Male with pre-NVP CD4 count >400 cells/mm^3 Certain HLA types are also associated with NVP-associated hepatic events but are population-specific.[a] Higher drug concentrations for PIs, particularly TPV.	Prevention: • Avoid concomitant use of hepatotoxic medications. • If hepatic enzymes are elevated >5 to 10 times ULN or chronic liver disease, most clinicians would avoid NVP. Monitoring: *For ARVs Other Than NVP:* • Obtain AST and ALT at baseline and thereafter at least every 3–4 months, or more frequently in at-risk patients (e.g., HBV- or HCV-coinfected or elevated baseline AST and ALT). *For NVP:* • Obtain AST and ALT at baseline, at 2 and 4 weeks, then every 3 months.	Asymptomatic patients with elevated ALT or AST should be evaluated for other causes and monitored closely (including repeating AST, ALT and checking total bilirubin). If ALT or AST is more than 5–10 times ULN and felt to be possibly or probably associated with ARVs, the potentially offending ARVs should be discontinued. In symptomatic patients, discontinue all ARVs and other potential hepatotoxic agents and avoid restarting the offending agent. If a symptomatic hepatic event occurs on NVP, permanently discontinue drug (see also NVP Hypersensitivity). When clinical hepatitis is associated with lactic acidosis, avoid restarting the most likely agent, including ZDV, d4T, and ddI in particular (see also Lactic Acidosis). Consider viral causes of hepatitis: HAV, HBV, HCV, EBV, and CMV.

Table 12e. Antiretroviral-Therapy-Associated Adverse Effects and Management Recommendations—Hepatic Events

(Last updated March 1, 2016; last reviewed March 1, 2016) (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)	Onset: • First months of therapy Presentation: • Jaundice; otherwise asymptomatic elevation of indirect bilirubin levels with normal AST, and ALT. Direct bilirubin may be normal or slightly elevated when levels of indirect bilirubin are very high.	HIV-Infected Children Receiving ATV: • In long-term follow-up, 9% had at least 1 total bilirubin level > 5 x ULN and 1.4% experienced jaundice	N/A	Monitoring: • No specific monitoring.	Not necessary to discontinue the offending agent except for cosmetic reasons. After an initial rise over the first few months of therapy, unconjugated bilirubin levels generally stabilize; in some patients, levels improve over time.
Non-Cirrhotic Portal Hypertension	ddI, d4t	Onset: • Generally after years of therapy Presentation: • GI bleeding, esophageal varices, hypersplenism • Mild elevations in AST and ALT, moderate increases in ALP, and pancytopenia (because of hypersplenism) • Liver biopsy may reveal a variety of findings, most commonly nodular regenerative hyperplasia or hepatoportal sclerosis.	Rare: • Probably less than 1%	Prolonged exposure to ARV therapy, especially ddI and the combination of ddI and d4T	Monitoring: • No specific monitoring	Manage complications of GI bleeding and esophageal varices. Discontinue/replace d4T or ddI, if patient is receiving either.

[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; ddI = 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

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Table 12f. Antiretroviral-Therapy-Associated Adverse Effects and Management Recommendations—Insulin Resistance, Asymptomatic Hyperglycemia, Diabetes Mellitus (Last updated March 1, 2016; last reviewed March 1, 2016)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
Insulin Resistance, Asymptomatic Hyperglycemia, DM[a]	Several NRTIs (e.g., d4T, ZDV, ddI) Several PIs (e.g., LPV/r; less often ATV, ATV/r, DRV/r, NFV, TPV/r)	Onset: • Weeks to months after beginning therapy; median of 60 days (adult data). Presentation *Most Commonly:* • Asymptomatic fasting hyperglycemia (possibly in the setting of lipodystrophy), metabolic syndrome, or growth delay *Also Possible:* • Frank DM (i.e., polyuria, polydipsia, polyphagia, fatigue, hyperglycemia)	Insulin Resistance *ARV-Treated Adults and Children:* • 6% to 33% Impaired Fasting Glucose *ARV-Treated Adults:* • 3% to 25% *ARV-Treated Children:* • 0% to 7% Impaired Glucose Tolerance *ARV-Treated Adults:* • 16% to 35% *ARV-Treated Children:* • 3% to 4% DM *ARV-Treated Adults:* • 0.6–4.7 per 100 person-years (2- to 4-fold greater than that for HIV-uninfected adults) *ARV-Treated Children:* • Rare in HIV-infected children	Risk Factors for Type 2 DM: • Lipodystrophy • Metabolic syndrome • Family history of DM • High BMI (obesity)	Prevention: • Lifestyle modification • Although uncertain, avoiding the use of d4T may reduce risk. Monitoring: • Monitor for polydipsia, polyuria, polyphagia, change in body habitus, and acanthosis nigricans. *Obtain RPG Levels at:* • Initiation of ARV therapy • 3–6 months after therapy initiation • Once a year thereafter *For RPG ≥140 mg/dL:* • Obtain FPG performed after 8-hour fast and consider referral to endocrinologist.	Counsel on lifestyle modification (e.g., a diet low in saturated fat, cholesterol, trans fat, and refined sugars; increased physical activity; cessation of smoking); consider consultation with dietician. Change NRTI (e.g., from d4T, ZDV, or ddI to TDF or ABC). For Either RPG ≥200 mg/dL Plus Symptoms of DM or FPG ≥126 mg/dL: • Patient meets diagnostic criteria for DM; consult endocrinologist. FPG 100–125 mg/dL: • Impaired FPG is suggestive of insulin resistance; consult endocrinologist FPG <100 mg/dL: *Normal FPG, but Does Not Exclude Insulin Resistance:* • Recheck FPG in 6–12 months.

[a] Insulin resistance, asymptomatic hyperglycemia, and DM form a spectrum of increasing severity. *Insulin resistance* is often defined as elevated insulin levels for the level of glucose observed; *impaired FPG* as an FPG of 100–125 mg/dL; *impaired glucose tolerance* as an elevated 2-hour PG of 140–199 mg/dL in a 75g-OGTT (or if <43 kg, 1.75 g/kg of glucose up to a maximum of 75g); 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; ATV = atazanavir; ATV/r = ritonavir-boosted atazanavir; BMI = body mass index; d4T = stavudine; ddI = didanosine; dL = deciliter; DM = diabetes mellitus; DRV/r = ritonavir-boosted darunavir; FPG = fasting plasma glucose; HgbA1c = glycosylated hemoglobin; LPV/r = ritonavir-boosted lopinavir; NFV = nelfinavir; NRTI = nucleoside reverse transcriptase inhibitor; OGTT = oral glucose tolerance test; PG = plasma glucose; PI = protease inhibitor; RPG = random plasma glucose; TDF = tenofovir disoproxil fumarate; TPV/r = ritonavir-boosted tipranavir; ZDV = zidovudine

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Table 12g. Antiretroviral-Therapy-Associated Adverse Effects and Management Recommendations—Lactic Acidosis

(Last updated March 1, 2016; last reviewed March 1, 2016)

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)	Onset: • 1–20 months after starting therapy (median onset 4 months in 1 case series) Presentation *Usually Insidious Onset of a Combination of Signs and Symptoms:* • Generalized fatigue, weakness, and myalgias • Vague abdominal pain, weight loss, unexplained nausea or vomiting • Dyspnea • Peripheral neuropathy **Note:** Patients may present with acute multi-organ failure (e.g., fulminant hepatic, pancreatic, respiratory failure).	Chronic, Asymptomatic Mild Hyperlactatemia (2.1–5.0 mmol/L) *Adults:* • 15% to 35% of adults receiving NRTI therapy for longer than 6 months *Children:* • 29% to 32% Symptomatic Severe Hyperlactatemia (>5.0 mmol/L) *Adults:* • 0.2% to 5.7% Symptomatic Lactic Acidosis/Hepatic Steatosis: • Rare in all age groups (1.3–11 episodes per 1000 person-years; increased incidence with the use of d4T/ddI when co-administered), but associated with a high fatality rate (33% to 58%)	Adults: • Female 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/mm^3 • Acquired riboflavin or thiamine deficiency • Possibly pregnancy Preterm Infants: • Exposure to propylene glycol (e.g., present as a diluent in LPV/r oral solution)	Prevention: • Avoid d4T and ddI individually; co-administration of d4T and ddI is not recommended in an ARV regimen (no exception). • Due to the presence of propylene glycol as a diluent, LPV/r oral solution should never be used in preterm neonates in the immediate postnatal period. • Monitor for clinical manifestations of lactic acidosis and promptly adjust therapy. Monitoring *Asymptomatic:* • Measurement of serum lactate is not recommended. *Clinical Signs or Symptoms Consistent with Lactic Acidosis:* • Obtain blood lactate level.[a] Additional diagnostic evaluations should include serum bicarbonate and anion gap and/or arterial blood gas, amylase and lipase, serum albumin, and hepatic transaminases.	Lactate 2.1–5.0 mmol/L (Confirmed with Second Test): • Consider replacing ddI and d4T with other ARVs. • As an alternative, temporarily discontinue all ARVs while conducting additional diagnostic workup. Lactate >5.0 mmol/L (Confirmed with Second Test)[b] or >10.0 mmol/L (Any 1 Test): • Discontinue all ARVs. • Provide supportive therapy (IV fluids; some patients may require sedation and respiratory support to reduce oxygen demand and ensure adequate oxygenation of tissues). Anecdotal (Unproven) Supportive Therapies: • Bicarbonate infusions, THAM, high-dose thiamine and riboflavin, oral antioxidants (e.g., L-carnitine, co-enzyme Q10, vitamin C) Following resolution of clinical and laboratory abnormalities, resume therapy, either with an NRTI-sparing regimen or a revised NRTI-containing regimen instituted with caution, using NRTIs less likely to inhibit mitochondria (ABC or TDF preferred; possibly FTC or 3TC), and monthly monitoring of lactate for at least 3 months.

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

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

Key to 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

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General Reviews

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Table 12h. Antiretroviral-Therapy-Associated Adverse Effects and Management Recommendations—Lipodystrophy, Lipohypertrophy, Lipoatrophy (Last updated March 1, 2016; last reviewed March 1, 2016) (page 1 of 2)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
Lipodystrophy (Fat Maldistribution) General Information	See below for specific associations.	Onset: • Trunk and limb fat initially increase within a few months of start of ART; peripheral fat wasting may not appear for 12 to 24 months after ART initiation.	Varies greatly depending upon measure and comparator group Highly Variable in Adults: • Up to 93% Children: • Up to 34%, perhaps more common in adolescents than prepubertal children	Genetic predisposition Puberty HIV-associated inflammation Older age Longer duration of ART Body habitus	See below.	See below Although more typically associated with certain ARVs (e.g., d4T), a regimen review with consideration of changing the regimen should be considered, whenever present
Central Lipohypertrophy or **Lipo-accumulation**	Can occur in the absence of ART, but most associated with PIs and EFV.	Presentation: • Central fat accumulation with increased abdominal girth, which may include dorsocervical fat pad (buffalo hump) and/or gynecomastia in males or breast hypertrophy in females, particularly with EFV. The appearance of central lipohypertrophy is accentuated in the presence of peripheral fat wasting (lipoatrophy).	Adults: • Up to 93% Children: • Up to 27%	Obesity before initiation of therapy Sedentary lifestyle	Prevention: • Calorically appropriate low-fat diet and exercise Monitoring: • 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 Data are Insufficient to Allow the Panel to Safely Recommend Use of Any of the Following Modalities in Children: • Recombinant human growth hormone • Growth hormone-releasing hormone • Metformin • Thiazolidinediones • Anabolic steroids • Liposuction.

Table 12h. Antiretroviral-Therapy-Associated Adverse Effects and Management Recommendations—Lipodystrophy, Lipohypertrophy, Lipoatrophy (Last updated March 1, 2016; last reviewed March 1, 2016) (page 2 of 2)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
Facial/Peripheral Lipoatrophy	Most associated with thymidine analogue NRTIs (d4T > ZDV)	Presentation: • Thinning of subcutaneous fat in face, buttocks, and extremities, measured as decrease in trunk/limb fat by DXA or triceps skinfold thickness. Preservation of lean body mass distinguishes lipoatrophy from HIV-associated wasting.	Adults: Up to 59% (particularly in patients on d4T-containing regimens) Children: • Up to 47% (particularly in patients on d4T-containing regimens) • Risk lower (up to 15%) in patients not treated with d4T or ZDV.	Underweight before ART	Prevention: • Avoid use of d4T and ZDV. Monitoring: • Patient self-report and physical exam are the most sensitive methods of monitoring lipoatrophy.	Replace d4T (not widely used and recommended only in special circumstances) or ZDV with other NRTIs if possible without loss of virologic control. Data are Insufficient to Allow the Panel to Safely Recommend Use of Any of the Following Modalities in Children: • Injections of poly-L-lactic acid • Recombinant human leptin • Autologous fat transplantation • 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; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; ZDV = zidovudine

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See the archived version of Supplement III, February 23, 2009 *Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection*, (http://www.aidsinfo.nih.gov) for a more complete discussion and reference list.

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Table 12i. Antiretroviral-Therapy-Associated Adverse Effects and Management Recommendations—Nephrotoxic Effects

(Last updated March 1, 2016; last reviewed March 1, 2016) (page 1 of 2)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
Urolithiasis/ Nephrolithiasis	ATV, IDV Although DRV causes crystalluria, it is not associated with increased nephrolithiasis risk.	Onset: • Weeks to months after starting therapy Clinical Findings: • Crystalluria, hematuria, pyuria, flank pain, sometimes increased creatinine	ATV-related nephrolithiasis occurs in <10%.	In adults, elevated urine pH (>5.7) Unknown in children	Prevention: • Maintain adequate hydration. Monitoring: • Obtain urinalysis at least every 6–12 months.	Provide adequate hydration and pain control; consider using alternative ARV.
Renal Dysfunction	TDF	Onset: • 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. Presentation: *More Common:* • Increased serum creatinine, proteinuria, normoglycemic glucosuria. Hypophosphatemia, usually asymptomatic; may present with bone and muscle pain, weakness. *Less Common:* • Renal failure, acute tubular necrosis, Fanconi syndrome, proximal renal tubulopathy, interstitial nephritis, nephrogenic diabetes insipidus with polyuria	Adults: • Approximately 2% with increased serum creatinine • Approximately 0.5% with severe renal complications Children: • Approximately 4% with hypophosphatemia or proximal tubulopathy; higher with prolonged TDF therapy, in advanced HIV infection or concomitant use of ddI	Risk May Be Increased in Children: • Aged >6 years • Black race, Hispanic/Latino ethnicity • Advanced HIV infection • 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. While unproven, routine monitoring intervals of every 3–6 months might be considered. Abnormal values should be confirmed by repeat testing, and frequency of monitoring can be increased if abnormalities are found and TDF is continued.	If TDF is the likely cause, consider using alternative ARV.

Table 12i. Antiretroviral-Therapy-Associated Adverse Effects and Management Recommendations—Nephrotoxic Effects

(Last updated March 1, 2016; last reviewed March 1, 2016) (page 2 of 2)

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

Key to Acronyms: ARV = antiretroviral; ATV = atazanavir; COBI = cobicistat; ddI = didanosine; DRV = darunavir; DTG = dolutegravir; GFR = glomerular filtration rate; IDV = indinavir; LPV/r = boosted lopinavir/ritonavir; PI = protease inhibitor; RPV = rilpivirine; TDF = tenofovir disoproxil fumarate

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Table 12j. Antiretroviral-Therapy-Associated Adverse Effects and Management Recommendations—Osteopenia and Osteoporosis (Last updated March 1, 2016; last reviewed March 1, 2016)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
Osteopenia and Osteoporosis	Any ART regimen Specific Agents of Possible Concern: • TDF • PIs, especially LPV/r	Onset: • Any age; more common in months after initiation of ART. Presentation: • Most commonly asymptomatic; fracture (rare) • Osteoporosis diagnosis in children requires clinical evidence of bone fragility (e.g., fracture with minimal trauma) and cannot rely solely on measured low BMD.	Low BMD: • 7% of a U.S. cohort had a BMD z score less than or equal to –2.0 (87% treated with ART). • 24% to 32% of Thai and Brazilian adolescents had a BMD z score less than or equal to –2.0 (92% to 100% treated with ART).	Longer duration of HIV infection Greater severity of HIV disease Growth delay, pubertal delay Low BMI Lipodystrophy Non-black race Smoking Prolonged systemic corticosteroid use Medroxyprog-esterone use Limited weight-bearing exercise	Prevention: • Ensure sufficient calcium and vitamin D intake. • Encourage weight-bearing exercise. • Minimize modifiable risk factors (e.g., smoking, low BMI, steroid use). Monitoring: • Assess nutritional intake (calcium, vitamin D, and total calories). • Consider obtaining serum 25-OH-vitamin D level.[a] • Obtain DXA.[b]	Ensure sufficient calcium intake and vitamin D sufficiency. Encourage weight-bearing exercise. Reduce modifiable risk factors (e.g., smoking, low BMI, use of steroids, use of medroxyprogesterone). Role of bisphosphonates not established in children Consider change in ARV regimen.

[a] Some experts would periodically measure 25-OH-vitamin D, especially in HIV-infected urban youth, 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

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Osteopenia and Osteoporosis

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Table 12k. Antiretroviral-Therapy-Associated Adverse Effects and Management Recommendations—Peripheral Nervous System Toxicity (Last updated March 1, 2016; last reviewed March 1, 2016)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency[a]	Risk Factors	Prevention/ Monitoring	Management
ARV Toxic Neuropathy[b]	d4T, ddI PIs	Onset: • Variable; weeks to months following NRTI initiation. Presentation: • Decreased sensation • Aching, burning, painful numbness • Hyperalgesia (lowered pain threshold) • Allodynia (non noxious stimuli cause pain) • Decreased or absent ankle reflexes Distribution: • Bilateral soles of feet, ascending to legs and fingertips	HIV-Infected Children: • 1.13% prevalence (baseline 2001); incidence 0.23 per 100 person-years (2001–2006) in a U.S. cohort. • <1% discontinued d4T because of neuropathy in 3 large African cohorts (aged 1 month–18 years; median follow-up 1.8–3.2 years). • 42 out of 174 (24%) in a South African cohort were diagnosed with peripheral neuropathy. 86% were taking d4T, and use of ddI was an additional risk factor. • 4/40 (10%) Indian children taking d4T had abnormal nerve conduction tests. HIV-Infected Adults on d4T: • Prevalence up to 57% • Incidence rates of 6.4–12.1 per 100 person-years	HIV-Infected Adults: • Preexisting neuropathy (e.g., diabetes, alcohol abuse, vitamin B-12 deficiency) • Elevated triglyceride levels • Older age • Poor nutrition • More advanced HIV disease • Concomitant use of other neurotoxic agents (e.g., INH) • Some mitochondrial DNA haplogroups may have increased risk.	Limit use of d4T and ddI. As part of routine care, monitor for symptoms and signs of peripheral neuropathy.	Discontinue offending agent. Persistent pain can be difficult to treat; topical capsaicin 8% may be helpful. Consider referral to a neurologist. Data Are Insufficient to Allow the Panel to Recommend Use of Any of the Following Modalities in Children: • Tricyclic antidepressants • Gabapentin • Pregabalin • Mexiletine • Lamotrigine • Acupuncture or other complementary approaches

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

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

Key to Acronyms: ARV = antiretroviral; d4T = stavudine; ddI = didanosine; INH = isoniazid; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor

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Table 12l. Antiretroviral-Therapy-Associated Adverse Effects and Management Recommendations—Rash and Hypersensitivity Reactions (Last updated March 1, 2016; last reviewed March 1, 2016) (page 1 of 4)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
Rash	Any ARV can cause rash.	Onset: • First few days to weeks after starting therapy Presentation: • Most rashes are mild-to-moderate, diffuse maculopapular eruptions. **Note:** Some rashes are the initial manifestation of systemic hypersensitivity (see Systemic HSR, SJS/TEN/EM Major).	Common (>10% Adults and/or Children): • NVP, EFV, ETR, FPV, FTC Less Common (5% to 10%): • ABC, DRV, TPV, TDF Unusual (2% to 4%): • LPV/r, RAL, MVC, RPV	• Sulfonamide allergy is a risk factor for rash with PIs containing a sulfonamide moiety (FPV, DRV, and TPV). • Possible association of polymorphisms in CYP2B6 and multiple HLA loci with rash with NVP.	When Starting NVP or Restarting After Interruptions >14 Days: • Once-daily dosing (50% of total daily dose) for 2 weeks, then escalation to target dose with twice-daily dosing is associated with fewer rashes.[a] • Avoid the use of systemic corticosteroids during NVP dose escalation. • Assess patient for rash severity, mucosal involvement, and other signs of systemic reaction. • Consider concomitant medications and illnesses that cause rash.	Mild-to-Moderate Maculopapular Rash Without Systemic or Mucosal Involvement: • Most will resolve without intervention; ARVs can be continued while monitoring.[a] • Antihistamines may provide some relief. Severe Rash (e.g., Blisters, Bullae, Ulcers, Skin Necrosis) and/or Rash Accompanied by Systemic Symptoms (e.g., Fever, Arthralgias, Edema) and/or Rash Accompanied by Mucous Membrane Involvement (e.g., Conjunctivitis): • Manage as SJS/TEN/EM major (see below). Rash in Patients Receiving NVP: • Given elevated risk of HSR, measure hepatic transaminases. • If hepatic transaminases are elevated, NVP should be discontinued and not restarted (see HSR-NVP).
	ENF	Onset: • First few days to weeks after starting therapy Presentation: • Local injection site reactions with pain, erythema, induration, nodules and cysts, pruritus, ecchymosis. Often multiple reactions at the same time.	Adults and Children: • >90%	Unknown	• Routinely assess patient for local reactions. • Rotate injection sites. • Massage area after injection.	• Continue the agent as tolerated by the patient. • Ensure patient is injecting as per instructions. • Rotate injection sites.

Table 12I. Antiretroviral-Therapy-Associated Adverse Effects and Management Recommendations—Rash and Hypersensitivity Reactions (Last updated March 1, 2016; last reviewed March 1, 2016) (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 frequency column)	Onset: • First few days to weeks after initiating therapy Presentation: • Initial rash may be mild, but often becomes painful, evolving to blister/bulla formation with necrosis in severe cases. Usually involves mucous membrane ulceration and/or conjunctivitis. Systemic symptoms may include fever, tachycardia, malaise, myalgia, and arthralgia.	Infrequent: • NVP (0.3%), EFV (0.1%), ETR (<0.1%) Case Reports: • FPV, ABC, DRV, ZDV, ddI, IDV, LPV/r, ATV, RAL	Adults: • Female gender • Race/ ethnicity (black, Asian, Hispanic)	To Lower the Risk of Reactions to NVP when Starting or Restarting after Interruptions >14 Days: • Utilize once-daily dosing (50% of total daily dose) for 2 weeks, then escalate to target dose with twice-daily dosing, which is associated with fewer rashes.[a] • Counsel families to report symptoms as soon as they appear.	• Discontinue all ARVs and other possible causative agents such as cotrimoxazole. • Provide intensive supportive care, IV hydration, aggressive wound care, pain management, antipyretics, parenteral nutrition, and antibiotics as needed in case of superinfection. • Corticosteroids and/or IVIG are sometimes used, but use of each is controversial. • Do not reintroduce the offending medication. • In case of SJS/TEN/EM major with one NNRTI, many experts would avoid use of other NNRTIs.
DRESS	EFV, ETR, NVP, RAL, RPV, DRV	Onset: • 1–8 weeks Presentation: • Fever • lymphadenopathy • facial swelling • a morbilliform to polymorphous rash • peripheral eosinophilia • atypical circulating lymphocytes • internal organ involvement (particularly liver and/or renal)	Rare	Unknown	• Obtain CBC, AST, ALT and creatinine in patient presenting with suggestive symptoms.	• Discontinue all ARVs and other possible causative agents such as cotrimoxazole. • Role for steroids unclear; suggest consultation with specialist. • Supportive care for end-organ disease • Do not reintroduce the offending medication.
Systemic HSR With or without skin involve-ment and excluding SJS/TEN	ABC	Onset *With First Use:* • Within first 6 weeks *With Re-Introduction:* • Within hours Presentation: • Symptoms include high fever, diffuse	2.3% to 9% (varies by racial/ethnic group).	• HLA-B*5701 (HSR very uncommon in people who are HLA-B*5701-neg ative); also HLA-DR7,	• Screening for HLA-B*5701. **ABC should not be prescribed if HLA-B*5701 is positive**. The medical record should clearly indicate that ABC is contraindicated. • When starting ABC, counsel patients and families about the signs	• 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 12l. Antiretroviral-Therapy-Associated Adverse Effects and Management Recommendations—Rash and Hypersensitivity Reactions (Last updated March 1, 2016; last reviewed March 1, 2016) (page 3 of 4)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
Systemic HSR With or without skin involvement and excluding SJS/TEN		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 re-challenge, symptoms can mimic anaphylaxis.		HLA-DQ3. • HSR risk is higher in those of white race compared to those of black or East Asian race.	and symptoms of HSR to ensure prompt reporting of reactions.	
	NVP	Onset: • Most frequent in the first few weeks of therapy but can occur through 18 weeks. Presentation: • Flu-like symptoms (including nausea, vomiting, myalgia, fatigue, fever, abdominal pain, jaundice) with or without skin rash that may progress to hepatic failure with encephalopathy.	4% (2.5% to 11%)	Adults: • Treatment-naive with higher CD4 count (>250 cells/mm^3 in women; >400 cells/mm^3 in men). • Female gender (risk is 3-fold higher in females compared with males). Children: • NVP hepatotoxicity and HSR are less common in pre-pubertal children than in adults. 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%.	When Starting NVP or Restarting After Interruptions >14 Days: • 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/mm^3 and in men with CD4 counts >400 cells/mm^3 unless benefits outweigh risks. • Do not use NVP in PEP.	• 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.

Table 12I. Antiretroviral-Therapy-Associated Adverse Effects and Management Recommendations—Rash and Hypersensitivity Reactions (Last updated March 1, 2016; last reviewed March 1, 2016) (page 4 of 4)

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

[a] The prescribing information for NVP states that patients experiencing rash during the 14-day lead-in period should not have the NVP dose increased until the rash has resolved. However, prolonging the lead-in phase beyond 14 days may increase risk of NVP resistance because of sub-therapeutic drug levels. Management of children who have persistent mild or moderate rash after the lead-in period should be individualized and 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; CD4 = CD4 T lymphocyte cell; ddI = didanosine; DRESS = drug rash with eosinophilia and systemic symptoms; DRV = darunavir; EFV = efavirenz; EM = erythema multiforme; ENF = enfuvirtide; ETR = etravirine; FPV = fosamprenavir; FTC = emtricitabine; HSR = hypersensitivity reaction; IDV = indinavir; IV = intravenous; IVIG = intravenous immune globulin; LPV/r = lopinavir/ritonavir; MVC = maraviroc; NNRTI = non-nucleoside reverse transcriptase inhibitor; NVP = nevirapine; 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

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Table 13: 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)	Current 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 ddI (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.
	Adolescence	Pubertal maturity (i.e., SMR IV or V)	TDF ABC	Once-daily dosing. Less long-term mitochondrial toxicity. Co-formulation with other ARV drugs can further reduce pill burden.
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.
PIs				
LPV/r Twice Daily[1]	≥1 year	≥3 kg	RAL or ATV/r	Better palatability. Less adverse lipid effect. Lower pill burden. Once-daily dosing (ATV/r).
	≥3 years	N/A	ATV/r EFV DRV/r RAL	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 <3 years.
	≥12 years	≥40 kg	DRV/r ATV/r DTG	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 • TDF/FTC/RPV • ABC/3TC/DTG	Once-daily dosing. Single pill. Alignment with adult regimens.

[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 effects, d4T may 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; ddI = didanosine; DRV/r = darunavir/ritonavir; DTG = dolutegravir; EFV = efavirenz; EVG = elvitegravir; FTC = emtricitabine; LPV/r = lopinavir/ritonavir; RAL = raltegravir; RPV=rilpivirine; SMR= sexual maturity rating (Tanner stage); TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; ZDV = zidovudine

Table 14: Discordance Among Virologic, Immunologic, and Clinical Responses

Differential Diagnosis of Poor Immunologic Response Despite Virologic Suppression
Poor Immunologic Response Despite Virologic Suppression and Good Clinical Response: • Lab error (in CD4 or viral load result) • Misinterpretation of normal, age-related CD4 decline (i.e., 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 Poor Immunologic and Clinical Responses Despite Virologic Suppression: • 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
• 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

Management of Virologic Treatment Failure

Since almost all ARV management decisions for treatment failure are based on addressing virologic failure, this section on managing treatment failure will address only virologic treatment failure (i.e., repeated plasma viral load >200 copies/mL after 6 months of therapy).

The approach to management and subsequent treatment of virologic treatment failure may differ depending on the etiology of the problem. Although the cause of virologic treatment failure may be multifactorial, it is generally the result of nonadherence. Assessment of a child with suspicion of virologic treatment failure should include evaluation of adherence to therapy, medication intolerance, pharmacokinetic (PK) explanations of low drug levels or elevated, potentially toxic levels, and evaluation of suspected drug resistance (see Antiretroviral Drug-Resistance Testing in the Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents). The main barrier to long-term maintenance of sustained virologic suppression in adults and children is incomplete adherence to medication regimens, with subsequent emergence of viral mutations conferring partial or complete resistance to one or more of the components of the ARV regimen. Table 15 outlines a comprehensive approach to evaluating causes of virologic treatment failure in children, with particular attention to adherence.

Table 15. Assessment of Causes of Virologic Antiretroviral Treatment Failure (page 1 of 2)

Cause of Virologic Treatment Failure	Assessment Method	Intervention
Nonadherence	1. Interview child and caretaker. • Take 24-hour or 7-day recall. • Obtain description of: • **Who** gives medications • **When** medications are taken/given • **What** medications are taken/given (names, doses) • **Where** medications are kept/administered • **How** medications make child feel, including ability to swallow meds • Have open-ended discussion of experiences taking/giving medications and barriers/ challenges.	• Identify or reengage family members to support/supervise adherence. • Establish fixed daily times and routines for medication administration. • To avoid any patient/caregiver confusion with drug names, explain that drug therapies have generic names and trade names, and many agents are coformulated under a third or fourth name. • Explore opportunities for facility or home-based DOT.
	2. Review pharmacy records. • Assess timeliness of refills. • Ensure that all ARVs are dispensed.	
	3. Observe medication administration. • Observe dosing/administration in clinic. • Conduct home-based observation by visiting health professional. • Admit to hospital for trial of therapy. • Observe administration/tolerance. • Monitor treatment response.	• Simplify medication regimen, if feasible. • Substitute new agents if single ARV is poorly tolerated. • Consider DOT. • Use tools to simplify administration (e.g., pill boxes, reminders [including alarms, cell phone apps], integrated medication packaging for a.m. or p.m. dosing). • As a last resort, consider gastric tube placement to facilitate adherence.
	4. Conduct psychosocial assessment. • Make a comprehensive, family-focused assessment of factors likely to impact adherence with particular attention to recent changes in: • Status of caregiver, housing, financial stability of household, child/caretaker relationships, school, and child's achievement level • Substance abuse (child, caretaker, family members) • Mental health and behavior • Child/youth and caretaker beliefs about ART • Disclosure status (to child and others) • Peer pressure	• Address competing needs through appropriate social services. • Address and treat concomitant mental illness and behavioral disorders. • Initiate disclosure discussions with family/child. • Consider need for child protective services and alternate care settings when necessary.
Pharmacokinetics and Dosing Issues	1. Recalculate doses for individual medications using weight or BSA. 2. Identify concomitant medications including prescription, over-the-counter, and recreational substances; assess for drug-drug interactions. 3. Consider drug levels for specific ARV drugs (see Role of Therapeutic Drug Monitoring).	• Adjust drug doses. • Discontinue or substitute competing medications. • Reinforce applicable food restrictions.

Table 15. Assessment of Causes of Virologic Antiretroviral Treatment Failure (page 2 of 2)

Cause of Virologic Treatment Failure	Assessment Method	Intervention
ARV Drug Resistance	1. Perform resistance testing, as appropriate (see Antiretroviral Drug-Resistance Testing in the Adult and Adolescent Antiretroviral Guidelines).	• If no resistance to current drugs is detected, focus on improving adherence. • If resistance to current regimen is detected, optimize adherence and evaluate potential for new regimen (see Management of Virologic Treatment Failure).

Key to Acronyms: ARV = antiretroviral; ART = antiretroviral therapy; BSA = body surface area; DOT = directly observed therapy

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	• 2 NRTIs plus PI • 2 NRTIs plus INSTI
2 NRTIs plus PI	• 2 NRTIs plus NNRTI • 2 NRTIs plus INSTI • 2 NRTIs plus different RTV-boosted PI • NRTI(s) plus INSTI plus (NNRTI or different RTV-boosted PI)
3 NRTIs	• 2 NRTIs plus NNRTI • 2 NRTIs plus PI • 2 NRTIs plus INSTI • INSTI plus 2 other active agents (chosen from NNRTI, PI, NRTI[s])
Failed Regimen(s) That Included NRTI(s), NNRTI(s), and PI(s)	• 2 NRTIs plus INSTI (plus RTV-boosted PI if additional active drug needed) • NRTI(s) plus RTV-boosted PI plus INSTI (consider adding T20 and/or MVC[b] if additional active drug[s] needed) • NRTI(s) plus RTV-boosted DRV or LPVplus ETR (consider adding one or more of INSTI, MVC,[b] or T20 if additional active drug[s] needed) • >1 NRTI plus 2 RTV-boosted PIs (LPV/r plus ATV) (consider adding an INSTI or T20 if additional active drug[s] needed)

[a] ARV regimens should be chosen based on treatment history and drug-resistance testing to optimize ARV drug effectiveness. This is particularly important in selecting NRTI components of an NNRTI-based regimen where drug resistance to the NNRTI can occur rapidly if the virus is not sufficiently sensitive to the NRTIs. Regimens should contain at least two, but preferably three, fully active drugs for durable, potent virologic suppression. **Please see individual drug profiles for information about drug interactions and dose adjustment when devising a regimen for children with multi-class drug resistance.** Collaboration with a pediatric HIV specialist is especially important when choosing regimens for children with multi-class drug resistance. Regimens in this table are provided as examples, but the list is not exhaustive.

[b] No current FDA-approved pediatric indication for maraviroc

Key to Acronyms: ATV = atazanavir; DRV = darunavir; ETR = etravirine; INSTI = integrase strand transfer inhibitor; LPV = lopinavir; LPV/r = lopinavir/ritonavir; MVC = maraviroc; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; RTV = ritonavir; T20 = enfuvirtide

Table 17. Target Trough Concentrations of Antiretroviral Drugs Relevant to Pediatric Populations[a] (page 1 of 2)

Drug	Concentration (ng/mL)
Established Efficacy Plasma Trough Concentrations	
Atazanavir	150
Fosamprenavir	400[b]
Lopinavir	1,000
Nelfinavir[c]	800

Drug	Concentration (ng/mL)
Established Efficacy Plasma Trough Concentrations	
Efavirenz	1,000
Nevirapine	3,000
Maraviroc	>50[d]
Tipranavir	20,500[d]

[a] Adapted from: Department of Health and Human Services. *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents.* 2014.

[b] Measurable amprenavir concentration

[c] Measurable active (M8) metabolite

[d] Suggested median plasma trough concentration in treatment-experienced patients with resistant HIV-1 strain only