Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

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

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/Monitoring	Management
Rash	Any ARV can cause rash	Onset: • First few days to weeks after starting therapy Presentation: • Most rashes are mild-to-moderate, diffuse maculopapular eruptions. **Note:** A rash can be 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) • Polymorphisms in CYP2B6 and multiple HLA loci may confer increased risk of rash with NVP.	When Starting NVP or Restarting After Interruptions >14 Days: • Utilize once-daily lead-in dosing (see NVP section).[a] • Avoid the use of systemic corticosteroids during NVP dose escalation. • Assess patient for rash severity, mucosal involvement, and other signs of systemic reaction.	Mild-to-Moderate Maculopapular Rash Without Systemic or Mucosal Involvement: • Most will resolve without intervention; ARVs can be continued while monitoring.[a] • Antihistamines may provide some relief. Severe Rash (e.g., Blisters, Bullae, Ulcers, Skin Necrosis) and/or Rash Accompanied by Systemic Symptoms (e.g., Fever, Arthralgia, Edema) and/or Rash Accompanied by Mucous Membrane Involvement (e.g., Conjunctivitis): • Manage as SJS/TEN/EM major (see below). Rash in Patients Receiving NVP: • Given elevated risk of HSR, measure hepatic transaminases. • If hepatic transaminases are elevated, NVP should be discontinued and not restarted (see HSR-NVP).
	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 13l. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Rash and Hypersensitivity Reactions (Last updated April 27, 2017; last reviewed April 27, 2017) (page 2 of 4)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/Monitoring	Management
SJS/TEN/EM Major	Many ARVs, especially NNRTIs (see Estimated Frequency column)	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 also include fever, tachycardia, malaise, myalgia, and arthralgia.	Infrequent: • NVP (0.3%), EFV (0.1%), ETR (<0.1%) Case Reports: • FPV, ABC, DRV, ZDV, ddI, IDV, LPV/r, ATV, RAL	Adults: • Female gender • Race/ethnicity (black, Asian, Hispanic)	When Starting NVP or Restarting After Interruptions >14 Days: • Utilize once-daily lead-in dosing (see NVP section).[a] • Counsel families to report symptoms as soon as they appear.	• Discontinue all ARVs and other possible causative agents such as TMP-SMX. • Provide intensive supportive care, IV hydration, aggressive wound care, pain management, antipyretics, parenteral nutrition, and antibiotics as needed in case of superinfection. • Corticosteroids and/or IVIG are sometimes used, but use of each is controversial. • Do not reintroduce the offending medication. • In case of SJS/TEN/EM major with one NNRTI, many experts would avoid use of other NNRTIs.
DRESS	EFV, ETR, NVP, RAL, RPV, DRV	Onset: • 1–8 weeks Presentation: • Fever • Lymphadenopathy • Facial swelling • Morbilliform to polymorphous rash • Peripheral eosinophilia • Atypical circulating lymphocytes • Internal organ involvement (particularly liver and/or renal)	Rare	Unknown	• Obtain CBC, AST, ALT and creatinine in patient presenting with suggestive symptoms.	• Discontinue all ARVs and other possible causative agents such as TMP-SMX. • Role for steroids unclear; suggest consultation with specialist. • Supportive care for end-organ disease • Do not reintroduce the offending medication.

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

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/Monitoring	Management
HSR With or without skin involvement and excluding SJS/TEN	ABC	Onset *With First Use:* • Within first 6 weeks *With Reintroduction:* • Within hours Presentation: • Symptoms include high fever, diffuse skin rash, malaise, nausea, headache, myalgia, arthralgia, diarrhea, vomiting, abdominal pain, pharyngitis, respiratory symptoms (e.g., dyspnea). • Symptoms worsen to include hypotension and vascular collapse with continuation. With rechallenge, symptoms can mimic anaphylaxis.	2.3% to 9% (varies by racial/ethnic group).	• HLA-B*5701 (HSR very uncommon in people who are HLA-B*5701-negative); also HLA-DR7, HLA-DQ3. • HSR risk is higher in those of white race compared to those of black or East Asian race.	• Screen for HLA-B*5701. **ABC should not be prescribed if HLA-B*5701 is present.** The medical record should clearly indicate that ABC is contraindicated. • When starting ABC, counsel patients and families about the signs and symptoms of HSR to ensure prompt reporting of reactions.	• Discontinue ARVs and investigate for other causes of the symptoms (e.g., a concurrent viral illness). • Treat symptoms as necessary. • Most symptoms resolve within 48 hours after discontinuation of ABC. • Do not rechallenge with ABC even if the patient is HLA-B*5701-negative.

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

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/Monitoring	Management
HSR With or without skin involvement and excluding SJS/TEN	NVP	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.
	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; CBC = complete blood count; CD4 = CD4 T lymphocyte cell; ddI = didanosine; DRESS = drug rash with eosinophilia and systemic symptoms; DRV = darunavir; DTG = dolutegravir; EFV = efavirenz; EM = erythema multiforme; ENF = enfuvirtide; ETR = etravirine; FPV = fosamprenavir; FTC = emtricitabine; HLA = human leukocyte antigen; HSR = hypersensitivity reaction; IDV = indinavir; IV = intravenous; IVIG = intravenous immune globulin; LPV/r = lopinavir/ritonavir; MVC = maraviroc; NNRTI = non-nucleoside reverse transcriptase inhibitor; NVP = nevirapine; PEP = post-exposure prophylaxis; PI = protease inhibitor; RAL = raltegravir; RPV = rilpivirine; SJS = Stevens-Johnson syndrome; TDF = tenofovir disoproxil fumarate; TEN = toxic epidermal necrolysis; TPV = tipranavir; ZDV = zidovudine

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