



Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

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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 1 of 4)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/Monitoring	Management
Rash	Any ARV can cause rash.	<p><u>Onset:</u></p> <ul style="list-style-type: none"> First few days to weeks after starting therapy <p><u>Presentation:</u></p> <ul style="list-style-type: none"> Most rashes are mild-to-moderate, diffuse maculopapular eruptions. <p>Note: Some rashes are the initial manifestation of systemic hypersensitivity (see Systemic HSR, SJS/TEN/EM Major).</p>	<p><u>Common (>10% Adults and/or Children):</u></p> <ul style="list-style-type: none"> NVP, EFV, ETR, FPV, FTC <p><u>Less Common (5% to 10%):</u></p> <ul style="list-style-type: none"> ABC, DRV, TPV, TDF <p><u>Unusual (2% to 4%):</u></p> <ul style="list-style-type: none"> LPV/r, RAL, MVC, RPV 	<ul style="list-style-type: none"> Sulfonamide allergy is a risk factor for rash with PIs containing a sulfonamide moiety (FPV, DRV, and TPV). Possible association of polymorphisms in CYP2B6 and multiple HLA loci with rash with NVP. 	<p><u>When Starting NVP or Restarting After Interruptions >14 Days:</u></p> <ul style="list-style-type: none"> 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. 	<p><u>Mild-to-Moderate Maculopapular Rash Without Systemic or Mucosal Involvement:</u></p> <ul style="list-style-type: none"> Most will resolve without intervention; ARVs can be continued while monitoring.^a Antihistamines may provide some relief. <p><u>Severe Rash (e.g., Blisters, Bullae, Ulcers, Skin Necrosis) and/or Rash Accompanied by Systemic Symptoms (e.g., Fever, Arthralgias, Edema) and/or Rash Accompanied by Mucous Membrane Involvement (e.g., Conjunctivitis):</u></p> <ul style="list-style-type: none"> Manage as SJS/TEN/EM major (see below). <p><u>Rash in Patients Receiving NVP:</u></p> <ul style="list-style-type: none"> Given elevated risk of HSR, measure hepatic transaminases. If hepatic transaminases are elevated, NVP should be discontinued and not restarted (see HSR-NVP).
	ENF	<p><u>Onset:</u></p> <ul style="list-style-type: none"> First few days to weeks after starting therapy <p><u>Presentation:</u></p> <ul style="list-style-type: none"> Local injection site reactions with pain, erythema, induration, nodules and cysts, pruritus, ecchymosis. Often multiple reactions at the same time. 	<p><u>Adults and Children:</u></p> <ul style="list-style-type: none"> >90% 	Unknown	<ul style="list-style-type: none"> Routinely assess patient for local reactions. Rotate injection sites. Massage area after injection. 	<ul style="list-style-type: none"> Continue the agent as tolerated by the patient. Ensure patient is injecting as per instructions. Rotate injection sites.

Table 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)	<p><u>Onset:</u></p> <ul style="list-style-type: none"> • First few days to weeks after initiating therapy <p><u>Presentation:</u></p> <ul style="list-style-type: none"> • Initial rash may be mild, but often becomes painful, evolving to blister/bulla formation with necrosis in severe cases. Usually involves mucous membrane ulceration and/or conjunctivitis. Systemic symptoms may include fever, tachycardia, malaise, myalgia, and arthralgia. 	<p><u>Infrequent:</u></p> <ul style="list-style-type: none"> • NVP (0.3%), EFV (0.1%), ETR (<0.1%) <p><u>Case Reports:</u></p> <ul style="list-style-type: none"> • FPV, ABC, DRV, ZDV, ddI, IDV, LPV/r, ATV, RAL 	<p><u>Adults:</u></p> <ul style="list-style-type: none"> • Female gender • Race/ethnicity (black, Asian, Hispanic) 	<p><u>To Lower the Risk of Reactions to NVP when Starting or Restarting after Interruptions >14 Days:</u></p> <ul style="list-style-type: none"> • 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. 	<ul style="list-style-type: none"> • 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	<p><u>Onset:</u></p> <ul style="list-style-type: none"> • 1–8 weeks <p><u>Presentation:</u></p> <ul style="list-style-type: none"> • Fever • lymphadenopathy • facial swelling • a morbilliform to polymorphous rash • peripheral eosinophilia • atypical circulating lymphocytes • internal organ involvement (particularly liver and/or renal) 	Rare	Unknown	<ul style="list-style-type: none"> • Obtain CBC, AST, ALT and creatinine in patient presenting with suggestive symptoms. 	<ul style="list-style-type: none"> • Discontinue all ARVs and other possible causative agents such as 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 involvement and excluding SJS/TEN	ABC	<p><u>Onset</u></p> <p><i>With First Use:</i></p> <ul style="list-style-type: none"> • Within first 6 weeks <p><i>With Re-Introduction:</i></p> <ul style="list-style-type: none"> • Within hours <p><u>Presentation:</u></p> <ul style="list-style-type: none"> • Symptoms include high fever, diffuse 	2.3% to 9% (varies by racial/ethnic group).	<ul style="list-style-type: none"> • HLA-B*5701 (HSR very uncommon in people who are HLA-B*5701-negative); also HLA-DR7, 	<ul style="list-style-type: none"> • 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 	<ul style="list-style-type: none"> • Discontinue ARVs and investigate for other causes of the symptoms (e.g., a concurrent viral illness). • Treat symptoms as necessary. • Most symptoms resolve within 48 hours after discontinuation of ABC. • Do not rechallenge with ABC even if the patient is HLA-B*5701-negative.

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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	<u>Onset:</u> • Most frequent in the first few weeks of therapy but can occur through 18 weeks. <u>Presentation:</u> • 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%)	<u>Adults:</u> • 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). <u>Children:</u> • 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 \geq 15% compared to children with CD4 <15%.	<u>When Starting NVP or Restarting After Interruptions >14 Days:</u> • 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	<u>Onset:</u> • Any time during therapy. <u>Presentation:</u> • 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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