

Table 17k. Antiretroviral Therapy–Associated Adverse Effects and Management Recommendations—Rash and Hypersensitivity Reactions

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Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/Monitoring	Management
Rash	Any ARV drug can cause rash.	<p>Onset</p> <ul style="list-style-type: none"> First few days to weeks after starting new ARV drug(s) <p>Presentation</p> <ul style="list-style-type: none"> Most rashes are mild-to-moderate diffuse maculopapular eruptions. <p>Note: A rash can be the initial manifestation of systemic hypersensitivity (see the SJS/TEN/EM major and HSR sections below).</p>	<p>Common (>10%)</p> <ul style="list-style-type: none"> EFV ETR FTC NVP <p>Less Common (5% to 10%)</p> <ul style="list-style-type: none"> ABC ATV DRV TDF <p>Uncommon (2% to 4%)</p> <ul style="list-style-type: none"> BIC LPV/r MVC RAL RPV 	<ul style="list-style-type: none"> Sulfonamide allergy is a risk factor for rash in patients who are taking PIs that contain a sulfonamide moiety (i.e., DRV). Polymorphisms in CYP2B6 and multiple HLA loci are associated with an increased risk of rash in patients who are taking NVP. 	<p>When Starting NVP or Restarting NVP After Interruptions of >14 Days</p> <ul style="list-style-type: none"> Utilize once-daily lead-in dosing.^a This may not be necessary in children aged <2 years.^b Avoid the use of systemic corticosteroids during NVP dose escalation. Assess the patient for rash severity, mucosal involvement, and other signs of systemic reaction. 	<p>Mild-to-Moderate Maculopapular Rash Without Systemic or Mucosal Involvement</p> <ul style="list-style-type: none"> Most rashes will resolve without intervention; ARV drugs can be continued while monitoring.^a Antihistamines may provide some relief. <p>Severe Rash and/or Rash Accompanied by Systemic Symptoms</p> <ul style="list-style-type: none"> Manage as SJS/TEN/EM major, DRESS, or HSR, as applicable (see below). <p>Rash in Patients Receiving NVP</p> <ul style="list-style-type: none"> Given the elevated risk of HSR, measure hepatic transaminases. If hepatic transaminases are elevated, NVP should be discontinued and not restarted (see the HSR section below).

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SJS/TEN/EM Major	Many ARV drugs, especially NNRTIs (see the Estimated Frequency column)	<p>Onset</p> <ul style="list-style-type: none"> • First few days to weeks after starting new ARV drug(s) <p>Presentation</p> <ul style="list-style-type: none"> • Initial rash may be mild, but it often becomes painful, evolving to blister/bulla formation with necrosis in severe cases. Usually involves mucous membrane ulceration and/or conjunctivitis. • Systemic symptoms may also include fever, tachycardia, malaise, myalgia, and arthralgia. 	<p>Infrequent</p> <ul style="list-style-type: none"> • NVP (0.3%) • EFV (0.1%) • ETR (<0.1%) <p>Case Reports</p> <ul style="list-style-type: none"> • ABC • ATV • DRV • LPV/r • RAL • ZDV 	<p>Adults</p> <ul style="list-style-type: none"> • Female sex <p>Patients who are Black, Asian, or Hispanic are at higher risk.</p>	<p>When Starting NVP or Restarting NVP After Interruptions of >14 Days</p> <ul style="list-style-type: none"> • Utilize once-daily lead-in dosing.^a This may not be necessary in children aged <2 years.^b • Counsel families to report symptoms as soon as they appear. 	<ul style="list-style-type: none"> • Discontinue all ARV drugs and other possible causative agents (e.g., TMP-SMX). • Provide intensive supportive care, including IV hydration, aggressive wound care, eye care, labial adhesion preventive care, pain management, and antipyretics. Parenteral nutrition and antibiotics may also be necessary. • Corticosteroids and/or IVIG are sometimes used, but the use of these interventions is controversial. • Do not reintroduce the offending medication. • In cases where a patient experiences SJS/TEN/EM major while taking an NNRTI, many experts would avoid using other NNRTIs when restarting ART.

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DRESS	DRV, DTG, EFV, ETR, NVP, RAL, RPV, BIC	<p>Onset</p> <ul style="list-style-type: none"> • 1–8 weeks after starting new ARV drug(s) <p>Presentation</p> <ul style="list-style-type: none"> • Fever • Lymphadenopathy • Facial swelling • Morbilliform to polymorphous rash • Peripheral eosinophilia • Atypical circulating lymphocytes • Internal organ involvement (particularly the liver and/or kidneys) 	Rare	<ul style="list-style-type: none"> • Unknown • Potential association with HLA-B*53:01 and RAL-induced DRESS 	Obtain a CBC and AST, ALT, and creatinine levels from patients who present with suggestive symptoms.	<ul style="list-style-type: none"> • Discontinue all ARV drugs and other possible causative agents (e.g., TMP-SMX). • The role of systemic steroids or IVIG in treatment is unclear; consultation with a specialist is recommended. • Provide supportive care for end-organ disease. • Do not reintroduce the offending medication.

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<p>HSR</p> <p>With or without skin involvement and excluding SJS/TEN</p>	<p>ABC</p>	<p>Onset</p> <p><i>With First Use</i></p> <ul style="list-style-type: none"> • Within first 6 weeks of initiating ABC <p><i>With Reintroduction</i></p> <ul style="list-style-type: none"> • Within hours of initiating ABC <p>Presentation</p> <ul style="list-style-type: none"> • Symptoms include high fever, diffuse skin rash, malaise, nausea, headache, myalgia, arthralgia, diarrhea, vomiting, abdominal pain, pharyngitis, and respiratory symptoms (e.g., dyspnea). • With continuation of ABC, symptoms may progress to hypotension and vascular collapse. With rechallenge, symptoms can mimic anaphylaxis. 	<p><1% to 9% (varies by ethnicity)</p>	<ul style="list-style-type: none"> • HLA-B*5701 (HSR is very uncommon in people who are HLA-B*5701 negative.) • The prevalence of HLA-B*5701 is generally lower in people from Africa and East Asia. 	<ul style="list-style-type: none"> • Screen for HLA-B*5701. ABC should not be prescribed if HLA-B*5701 is present. The medical record should clearly indicate that ABC is contraindicated in these patients. • When starting ABC, counsel patients and families about the signs and symptoms of HSR to ensure prompt reporting of reactions. 	<ul style="list-style-type: none"> • Discontinue all ARV drugs and investigate other causes of the symptoms (e.g., a concurrent viral illness). • Provide symptomatic treatment. • Most symptoms resolve within 48 hours after discontinuing ABC. • Do not rechallenge with ABC even if the patient is HLA-B*5701 negative.

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	NVP	<p>Onset</p> <ul style="list-style-type: none"> Occurs most frequently in the first few weeks of therapy but can occur through 18 weeks. <p>Presentation</p> <ul style="list-style-type: none"> Flu-like symptoms (including nausea, vomiting, myalgia, fatigue, fever, abdominal pain, and jaundice) with or without skin rash that may progress to hepatic failure with encephalopathy 	Occurs in 4% of patients on average, with a range of 2.5% to 11%.	<p>Adults</p> <ul style="list-style-type: none"> ARV-naive with a higher CD4 count (>250 cells/mm³ in women; >400 cells/mm³ in men) Female sex (risk is threefold higher in females than in males) Hepatitis B or hepatitis C infection <p>Children</p> <ul style="list-style-type: none"> NVP hepatotoxicity and HSR are less common in prepubertal children than in adults, and both are uncommon in infants. 	<p>When Starting NVP or Restarting NVP After Interruptions of >14 Days</p> <ul style="list-style-type: none"> A 2-week lead-in period with once-daily dosing, followed by dose escalation to twice daily as recommended, may reduce the risk of reaction.^a This may not be necessary in children aged <2 years.^b Counsel families about signs and symptoms of HSR to ensure prompt reporting of reactions. 	<ul style="list-style-type: none"> Discontinue all ARV drugs. Consider other causes of hepatitis and discontinue all hepatotoxic medications. Provide supportive care as indicated and monitor the patient closely. Do not reintroduce NVP. It is unclear whether it is safe to use other NNRTIs after a patient experiences symptomatic hepatitis due to NVP, and many experts would avoid the NNRTI drug class when restarting treatment.

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				<ul style="list-style-type: none"> High CD4 percentage is associated with an increased risk of NVP toxicity. In the PREDICT Study, the risk of NVP toxicity (rash, hepatotoxicity, and hypersensitivity) was 2.65 times greater in children who had CD4 percentages $\geq 15\%$ than in children who had CD4 percentages $< 15\%$. 	<ul style="list-style-type: none"> Obtain AST and ALT levels in patients with rash. Obtain AST and ALT levels at baseline, before dose escalation, 2 weeks after dose escalation, and thereafter at 3-month intervals. Avoid NVP use in women with CD4 counts > 250 cells/mm³ and in men with CD4 counts > 400 cells/mm³, unless benefits outweigh risks. Do not use NVP as postexposure prophylaxis outside of the neonatal period. 	
	ETR	<p>Onset</p> <ul style="list-style-type: none"> Any time during therapy 	Rare	Unknown	Evaluate for hypersensitivity if the patient is symptomatic.	<ul style="list-style-type: none"> Discontinue all ARV drugs. Rechallenge with ETR is not recommended.

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		Presentation <ul style="list-style-type: none"> Symptoms may include rash, constitutional findings, and sometimes organ dysfunction, including hepatic failure. 				
	MVC	Rash preceding hepatotoxicity	Rare	Unknown	Obtain AST and ALT levels from patients with rash or other symptoms of hypersensitivity.	<ul style="list-style-type: none"> Discontinue all ARV drugs. Rechallenge with MVC is not recommended.
	DTG	Rash with hepatic dysfunction	Rare	Unknown	Obtain AST and ALT levels from patients with rash or other symptoms of hypersensitivity.	<ul style="list-style-type: none"> Discontinue all ARV drugs. Rechallenge with DTG is contraindicated.

^a The prescribing information for NVP states that patients who experience 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 the risk of NVP resistance because of subtherapeutic drug levels. Children who have persistent mild or moderate rash after the lead-in period should receive individualized care. Consult an expert in HIV care when managing these patients. **NVP should be stopped and not restarted** if the rash is severe or progressing. See the [Nevirapine](#) section of the Drug Appendix.

^b Lead-in dosing is **not recommended** when using NVP for either presumptive or definitive HIV therapy in newborns with perinatal HIV exposure or perinatal HIV infection. See the [Nevirapine](#) section of the Drug Appendix and [Table 13. Antiretroviral Management for Infants With *In Utero* or Intrapartum Exposure to HIV in Antiretroviral Management of Infants With *In Utero*, Intrapartum, or Breastfeeding Exposure to HIV.](#)

Key: ABC = abacavir; ALT = alanine transaminase; ART = antiretroviral therapy; ARV = antiretroviral; AST = aspartate aminotransferase; ATV = atazanavir; BIC = bictegravir; CBC = complete blood count; CD4 = CD4 T lymphocyte; CYP2B6 = cytochrome P450 family 2 subfamily B member 6; DRESS = drug reaction (or rash) with eosinophilia and systemic symptoms; DRV = darunavir; DTG = dolutegravir; EFV = efavirenz; EM = erythema multiforme; ETR = etravirine; FTC = emtricitabine; HLA = human leukocyte antigen; HLA-B*53:01 = human leukocyte antigen gene variant; HLA-B*5701 = human leukocyte antigen gene variant; HSR = hypersensitivity reaction; IV = intravenous; IVIG = intravenous immune globulin; LPV/r = lopinavir/ritonavir; MVC = maraviroc; NNRTI = non-nucleoside reverse transcriptase inhibitor; NVP = nevirapine; PI = protease inhibitor; PREDICT Study = Personalised Responses to Dietary Composition Trial Study; RAL = raltegravir; RPV = rilpivirine; SJS = Stevens-Johnson syndrome; TDF = tenofovir disoproxil fumarate; TEN = toxic epidermal necrolysis; TMP-SMX = trimethoprim-sulfamethoxazole; ZDV = zidovudine

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