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.	Onset • First few days to weeks after starting new ARV drug(s) Presentation • Most rashes mild to moderate diffuse maculopapular eruptions Note: A rash can be the initial manifestation of systemic hypersensitivity (see the SJS/TEN/EM major and HSR sections below).	Common (>10%) • EFV • ETR • FTC • NVP Less Common (5% to 10%) • ABC • ATV • DRV • TDF Unusual (2% to 4%) • BIC • LPV/r • MVC • RAL • RPV	• 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.	When Starting NVP or Restarting NVP After Interruptions of >14 Days • Utilize once-daily lead-in dosing.[a] This may not be necessary in children ages <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.	Mild-to-Moderate Maculopapular Rash Without Systemic or Mucosal Involvement • Most rashes will resolve without intervention; ARV drugs can be continued while monitoring.[a] • Antihistamines may provide some relief. Severe Rash and/or Rash Accompanied by Systemic Symptoms • Manage as SJS/TEN/EM major, DRESS, or HSR as applicable (see below). Rash in Patients Receiving NVP • Given the elevated risk of HSR, measure hepatic transaminases. • If hepatic transaminases are elevated, NVP should be discontinued and not

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						restarted (see the HSR section below).
SJS/TEN/EM Major	Many ARV drugs, especially NNRTIs (see the Estimated Frequency column)	Onset • First few days to weeks after starting new ARV drug(s) Presentation • 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.	Infrequent • NVP (0.3%) • EFV (0.1%) • ETR (<0.1%) Case Reports • ABC • ATV • DRV • LPV/r • RAL • ZDV	Adults • Female sex Patients who are Black, Asian, or Hispanic at higher risk	When Starting NVP or Restarting NVP After Interruptions of >14 Days • 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.	• 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.
DRESS	DRV, DTG, EFV, ETR, NVP, RAL, RPV	Onset • 1–8 weeks after starting new ARV drug(s).	Rare	• Unknown • Potential association with HLA-B*53:01	Obtain a CBC and AST, ALT, and creatinine levels from patients who present with suggestive symptoms.	• Discontinue all ARV drugs and other possible causative agents (e.g., TMP-SMX). • The role of systemic steroids or IVIG in treatment is

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		Presentation • Fever • Lymphadenopathy • Facial swelling • Morbilliform to polymorphous rash • Peripheral eosinophilia • Atypical circulating lymphocytes • Internal organ involvement (particularly the liver and/or kidneys)		and RAL-induced DRESS		unclear; consultation with a specialist is recommended. • Provide supportive care for end-organ disease. • Do not reintroduce the offending medication.
HSR With or without skin involvement and excluding SJS/TEN	ABC	Onset *With First Use* • Within first 6 weeks of initiating ABC *With Reintroduction* • Within hours of initiating ABC Presentation • Symptoms include high fever, diffuse skin rash, malaise,	<1% to 9% (varies by ethnicity)	• HLA-B*5701 (HSR is very uncommon in people who are HLA-B*5701 negative). • The risk of HSR is higher in patients who are white than in patients who are Black or East Asian.	• 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.	• 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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		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.				
	NVP	Onset • Occurs most frequently 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, and jaundice) with or without skin rash that may progress to hepatic	Occurs in 4% of patients on average, with a range of 2.5% to 11%.	Adults • ARV-naive with a higher CD4 count (>250 cells/mm^3 in women; >400 cells/mm^3 in men) • Female sex (risk is threefold higher in females than in males). Children • NVP hepatotoxicity and HSR are less common in prepubertal children than in adults, and	When Starting NVP or Restarting NVP After Interruptions of >14 Days • 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.	• 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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		failure with encephalopathy.		both are uncommon in infants. • 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 ≥15% than in children who had CD4 percentages <15%.	• 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/mm^3 and in men with CD4 counts >400 cells/mm^3, unless benefits outweigh risks. • Do not use NVP as PEP outside of the neonatal period.	
	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 all ARV drugs. • Rechallenge with ETR is not recommended.

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	MVC	Rash preceding hepatotoxicity	Rare	Unknown	Obtain AST and ALT levels from patients with rash or other symptoms of hypersensitivity.	• 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.	• 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 Drug Dosing Recommendations for Newborns in Antiretroviral Management of Newborns With Perinatal HIV Exposure or HIV Infection.

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*5701 = human leucocyte 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; PEP = post-exposure prophylaxis; 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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