
# Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection



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## Table 17I. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Rash, SJS/EM/TEN, HSR (page 1 of 4) (Last updated November 1, 2012; last reviewed November 1, 2012)

| Adverse Effects | Associated ARVs | Onset/Clinical Manifestations | Estimated Frequency | Risk Factors | Prevention/Monitoring | Management |
|---|---|---|---|---|---|---|
| Rash | Any ARV can cause rash. | Onset:<br>First few days to weeks after starting therapy<br><br>Presentation:<br>Most rashes are mild-to-moderate, diffuse maculopapular eruptions.<br><br>Some rashes are a manifestation of systemic hypersensitivity (see also HSR). | Common (>10% adults and/or children):<br>NVP, EFV, ETR, FPV, ATV, FTC<br><br>Less common (5%–10%):<br>ABC, DRV, TPV, TDF<br><br>Unusual (2%–4%):<br>LPV/r, RAL, MVC, RPV | • Sulfonamide allergy is a risk factor for rash with PIs containing a sulfonamide moiety (FPV, DRV, TPV).<br>• 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 use of corticosteroids during NVP dose escalation.<br>• Assess patient for concomitant medications and illnesses that cause rash, rash severity, mucosal involvement, and presence of systemic signs and symptoms (see also HSR). | *Mild-to-moderate maculopapular rash without systemic or mucosal involvement:*<br><br>Prescribe antihistamine as needed; ARV medication can be continued.[a]<br><br>*Severe rash (accompanied by blisters, fever, involvement of the mucous membranes, conjunctivitis, edema, arthralgias):*<br>• Discontinue all ARVs and other possible causative agents such as cotrimoxazole. Do not restart the offending medication. (See SJS/EM/TEN.)<br>• In case of SJS/EM/TEN with one NNRTI, many experts would avoid use of other NNRTIs.<br><br>If rash develops with NVP treatment, measure hepatic transaminases. If hepatic transaminases are elevated, NVP should be discontinued and not restarted (see NVP hypersensitivity). |
| | ENF | Onset:<br>First few days to weeks after starting therapy<br><br>Presentation:<br>Local injection site reactions with pain, erythema, induration, nodules and cysts, pruritis, ecchymosis. Often multiple reactions at the same time. | Adults and children: >90% | Unknown | • During routine visits, assess patient for local reactions.<br>• Rotate injection sites.<br>• Massage area after injection. | • Continue the agent as tolerated by the patient.<br>• Adjust injection technique.<br>• Rotate injection sites. |

## Table 17l. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Rash, SJS/EM/TEN, HSR (page 2 of 4) (Last updated November 1, 2012; last reviewed November 1, 2012)

| Adverse Effects | Associated ARVs | Onset/Clinical Manifestations | Estimated Frequency | Risk Factors | Prevention/Monitoring | Management |
|---|---|---|---|---|---|---|
| SJS/EM major/TEN | Many ARVs, especially NNRTIs (see frequency column) | Onset:<br>First few days to weeks after initiating therapy<br><br>Presentation:<br>Skin eruption occurs with mucous membrane ulceration, conjunctivitis. Can evolve into blister/bulla formation and can progress to skin necrosis. Systemic symptoms may include fever, tachycardia, malaise, myalgia, and arthralgia. | Infrequent:<br>NVP (0.3%), EFV (0.1%), ETR (<0.1%)<br><br>Case reports:<br>FPV, ABC, DRV, ZDV, ddI, IDV, LPV/r, ATV, RAL | Adults:<br>• Female gender<br>• Race/ethnicity (black, Asian, Hispanic) | • *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]<br>• Counsel families to report symptoms as soon as they appear. | • Discontinue all ARVs and other possible causative agents such as cotrimoxazole.<br>• Provide intensive supportive care, IV hydration, aggressive wound care, pain management, antipyretics, parenteral nutrition, and antibiotics as needed in case of superinfection.<br>• Corticosteroids and/or IVIG are sometimes used but use of each is controversial.<br>• Do not reintroduce the offending medication.<br>• In case of SJS/EM/TEN with one NNRTI, many experts would avoid use of other NNRTIs. |
| Systemic HSR (with or without skin involvement and excluding SJS) | ABC | Onset:<br>*With first use:*<br>within first 6 weeks<br><br>*With reintroduction:*<br>within hours<br><br>Presentation:<br>Symptoms include high fever, diffuse skin rash, malaise, nausea, headache, myalgia, arthralgia, diarrhea, vomiting, abdominal pain, pharyngitis, respiratory symptoms such as dyspnea. Symptoms worsen to include hypertension and vascular collapse with continuation. With rechallenge, symptoms can mimic anaphylaxis. | 2.3%–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.<br>• Whites are at much greater risk of HSR than blacks or Asians. | • Screen for HLA- B*5701. ABC should not be prescribed if HLA-B*5701 is positive. The medical record should clearly indicate that the patient is ABC allergic.<br>• 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, such as an intercurrent viral illness.<br>• Treat symptoms as necessary.<br>• Most symptoms resolve within 48 hours after discontinuation of ABC.<br>• Do not rechallenge with ABC even if the patient is HLA-B*5701 negative. |

## Table 17l. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Rash, SJS/EM/TEN, HSR (page 3 of 4) (Last updated November 1, 2012; last reviewed November 1, 2012)

| Adverse Effects | Associated ARVs | Onset/Clinical Manifestations | Estimated Frequency | Risk Factors | Prevention/Monitoring | Management |
|---|---|---|---|---|---|---|
| Systemic HSR (with or without skin involvement and excluding SJS) | NVP | Onset:<br>Most frequent in the first few weeks of therapy but can occur through 18 weeks.<br><br>Presentation:<br>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.<br><br>DRESS syndrome has also been described. | 4% (2.5%–11%) | Adults:<br>• Treatment-naive with higher CD4 count (>250 cells/mm$^3$ in women; >400 cells/mm$^3$ in men).<br>• Female gender (Risk is 3-fold higher in females compared with males.)<br><br>Children:<br>NVP hepatoxicitiy and hypersensitivity are less common in prepubertal children than in adults.<br>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%. | • 2-week lead-in period for start or restart for interruptions >14 days with once-daily dosing then dose escalation to twice daily as recommended may reduce rash and hepatic events.[a]<br>• Counsel families about signs and symptoms of HSR to ensure prompt reporting of reactions.<br>• 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.<br>• 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.<br>• Do not use NVP in postexposure prophylaxis. | • Discontinue ARVs.<br>• Consider other causes for hepatitis and discontinue all hepatotoxic medications.<br>• Provide supportive care as indicated and monitor patient closely.<br>• Do not reintroduce 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 17l. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Rash, SJS/EM/TEN, HSR (page 4 of 4) (Last updated November 1, 2012; last reviewed November 1, 2012)

| Adverse Effects | Associated ARVs | Onset/Clinical Manifestations | Estimated Frequency | Risk Factors | Prevention/Monitoring | Management |
|---|---|---|---|---|---|---|
| Systemic HSR (with or without skin involvement and excluding SJS) | ENF, ETR | Onset: Any time during therapy.<br>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 is not recommended. |
| | RAL | DRESS syndrome | Case report | Unknown | Evaluate for hypersensitivity if the patient is symptomatic. | Discontinue all ARVs.<br>Rechallenge with RAL 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.<br>Rechallenge with MVC is not recommended. |

[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 subtherapeutic 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 if the rash is severe or is worsening or progressing.

**Key to Acronyms:** ABC = abacavir, ALT = alanine transaminase, ARVs = antiretrovirals, AST = aspartate aminotransferase, ATV = atazanavir, 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, 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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