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)

<table>
<thead>
<tr>
<th>Adverse Effects</th>
<th>Associated ARVs</th>
<th>Onset/Clinical Manifestations</th>
<th>Estimated Frequency</th>
<th>Risk Factors</th>
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<tbody>
<tr>
<td>Rash</td>
<td>Any ARV can cause rash</td>
<td>Onset:</td>
<td>Common (&gt;10% Adults and/or Children): NVP, EFV, ETR, FPV, FTC</td>
<td>Sulfonamide allergy is a risk factor for rash with PIs containing a sulfonamide moiety (FPV, DRV, and TPV)</td>
<td>When Starting NVP or Restarting After Interruptions &gt;14 Days: Utilize once-daily lead-in dosing (see NVP section).^</td>
<td>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.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Presentation:</td>
<td>• Most rashes are mild-to-moderate, diffuse maculopapular eruptions.</td>
<td>• Polymorphisms in CYP2B6 and multiple HLA loci may confer increased risk of rash with NVP.</td>
<td>• Avoid the use of systemic corticosteroids during NVP dose escalation.</td>
<td>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).</td>
</tr>
<tr>
<td>ENF</td>
<td></td>
<td>Note: A rash can be the initial manifestation of systemic hypersensitivity (see Systemic HSR, SJS/TEN/EM Major)</td>
<td>Unusual (2% to 4%): LPV/r, RAL, MVC, RPV</td>
<td></td>
<td>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).</td>
<td>Continue the agent as tolerated by the patient. Ensure patient is injecting as per instructions. Rotate injection sites.</td>
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<tr>
<td></td>
<td></td>
<td>Adults and Children:</td>
<td>&gt;90%</td>
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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 2 of 4)

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| 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).  
• 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)

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| 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. |
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<td>HSR</td>
<td>NVP</td>
<td>Onset: Most frequent in the first few weeks of therapy but can occur through 18 weeks.</td>
<td>4% (2.5% to 11%)</td>
<td>Adults: Treatment-naive with higher CD4 count (&gt;250 cells/mm³ in women; &gt;400 cells/mm³ 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 &lt;15%.</td>
<td>When Starting NVP or Restarting After Interruptions &gt;14 Days: 2-week lead-in period with once-daily dosing then dose escalation to twice daily as recommended may reduce risk of reaction.° 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 &gt;250 cells/mm³ and in men with CD4 counts &gt;400 cells/mm³ unless benefits outweigh risks. Do not use NVP in PEP. Evaluate for hypersensitivity if the patient is symptomatic.</td>
<td>• 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.</td>
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<td></td>
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<td>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.</td>
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<td></td>
<td>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 &lt;15%.</td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>ENF, ETR</td>
<td></td>
<td>Onset: Any time during therapy.</td>
<td>Rare</td>
<td>Unknown</td>
<td></td>
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</tr>
<tr>
<td></td>
<td></td>
<td>Presentation: Symptoms may include rash, constitutional findings, and sometimes organ dysfunction including hepatic failure.</td>
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<tr>
<td>MVC</td>
<td></td>
<td>Rash preceding hepatotoxicity</td>
<td>Rare</td>
<td>Unknown</td>
<td>Obtain AST and ALT in patients with rash or other symptoms of hypersensitivity. Obtain AST and ALT in patients with rash or other symptoms of hypersensitivity.</td>
<td>Discontinue all ARVs • Rechallenge with MVC is not recommended.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Rash with hepatic dysfunction</td>
<td>Rare</td>
<td>Unknown</td>
<td>Obtain AST and ALT in patients with rash or other symptoms of hypersensitivity.</td>
<td>Discontinue all ARVs. • Rechallenge with DTG is contraindicated.</td>
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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

**References**


