Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

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# Table 15l. Antiretroviral-Therapy-Associated Adverse Effects and Management Recommendations—Rash and Hypersensitivity Reactions

(Last updated May 22, 2018; last reviewed May 22, 2018)

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<tr>
<th>Adverse Effects</th>
<th>Associated ARVs</th>
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</table>
| Rash            | Any ARV can cause rash | Onset:  
• First few days to weeks after starting new ARV(s)  
Presentation:  
• Most rashes are mild-to-moderate, diffuse maculopapular eruptions  
Note: A rash can be the initial manifestation of systemic hypersensitivity (see SJS/TEN/EM Major and HSR sections below). | Common (>10%  
Adults and/or Children):  
• NVP  
• EFV  
• ETR  
• FPV  
• FTC  
Less Common (5% to 10%):  
• ABC  
• DRV  
• TPV  
• TDF  
Unusual (2% to 4%):  
• LPV/r  
• RAL  
• MVC  
• RPV | • Sulfonamide allergy is a risk factor for rash with PIs containing a sulfonamide moiety (FPV, DRV, and TPV)  
• Polymorphisms in CYP2B6 and multiple HLA loci may confer increased risk of rash with NVP | When Starting NVP or Restarting After Interruptions >14 Days:  
• Utilize once-daily lead-in dosing (see NVP section).†  
• Avoid the use of systemic corticosteroids during NVP dose escalation.  
• Assess 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; ARVs can be continued while monitoring.†  
• Antihistamines may provide some relief.  
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)  
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 below). |  
| T-20            | Onset:  
• First few days to weeks after starting new ARV(s)  
Presentation:  
• Local injection site reactions with pain, erythema, induration, nodules and cysts, pruritus, and ecchymosis  
• Often multiple reactions at the same time | Children and Adults:  
• >90% | Unknown | • Routinely assess patient for local reactions.  
• Rotate injection sites.  
• Massage area after injection. |  

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<tr>
<td><strong>SJS/TEN/EM Major</strong></td>
<td>Many ARVs, especially NNRTIs (see Estimated Frequency column)</td>
<td>Onset:  • First few days to weeks after starting new ARV(s)</td>
<td>Infrequent:  • NVP (0.3%)  • EFV (0.1%)  • ETR (&lt;0.1%)</td>
<td>Adults:  • Female gender  • Race/ethnicity (black, Asian, Hispanic)</td>
<td>When Starting NVP or Restarting After Interruptions &gt;14 Days:  • Utilize once-daily lead-in dosing (see NVP section).³  • Counsel families to report symptoms as soon as they appear.</td>
<td>• Discontinue all ARVs and other possible causative agents (e.g., 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 occurring with 1 NNRTI, many experts would avoid use of other NNRTIs.</td>
</tr>
<tr>
<td><strong>DRESS</strong></td>
<td>EFV, ETR, NVP, RAL, RPV, DRV</td>
<td>Onset:  • 1–8 weeks after starting new ARV(s)</td>
<td>Rare</td>
<td>Unknown</td>
<td>• Obtain CBC, AST, ALT, and creatinine from a patient presenting with suggestive symptoms.</td>
<td>• Discontinue all ARVs and other possible causative agents (e.g., TMP-SMX).  • Role for steroids unclear; suggest consultation with specialist.  • Provide supportive care for end-organ disease.  • Do not reintroduce the offending medication.</td>
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<tr>
<td>HSR</td>
<td>ABC</td>
<td>Onset</td>
<td>2.3% to 9% (varies by ethnicity).</td>
<td>• HLA-B<em>5701 (HSR very uncommon in people who are HLA-B</em>5701-negative); combination of HLA-DR7 plus HLA-DQ3 also confers risk.</td>
<td>• Screen for HLA-B<em>5701. **ABC should not be prescribed if HLA-B</em>5701 is present.** The medical record should clearly indicate that ABC is <strong>contraindicated.</strong></td>
<td>• Discontinue ARVs and investigate for other causes of the symptoms (e.g., a concurrent viral illness).</td>
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<td>With First Use:</td>
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<td>• HSR risk is higher in those of white race compared to those of black or East Asian race.</td>
<td>• When starting ABC, counsel patients and families about the signs and symptoms of HSR to ensure prompt reporting of reactions.</td>
<td>• Treat symptoms as necessary.</td>
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<td></td>
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<td>Within first 6 weeks</td>
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<td>• Most symptoms resolve within 48 hours after discontinuation of ABC.</td>
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<td>With Reintroduction:</td>
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<td>• Do not rechallenge with ABC even if the patient is HLA-B*5701-negative.</td>
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<td>Within hours</td>
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<td>Presentation:</td>
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<td>Symptoms include high fever,</td>
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<td></td>
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<td>diffuse skin rash, malaise,</td>
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<td></td>
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<td>nausea, headache, myalgia,</td>
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<td>arthralgia, diarrhea,</td>
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<td>vomiting, abdominal pain,</td>
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<td>pharyngitis, and respiratory</td>
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<td>symptoms (e.g., dyspnea).</td>
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<td>Symptoms worsen to include</td>
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<td>hypotension and vascular</td>
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<td>collapse with continuation of</td>
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<td>ABC. With rechallenge,</td>
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<td>symptoms can mimic anaphylaxis.</td>
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<td>HSR</td>
<td>NVP</td>
<td>Onset:</td>
<td>4% (2.5% to 11%)</td>
<td>Adults:</td>
<td>When Starting NVP or Restarting After Interruptions &gt;14 Days:</td>
<td>• Discontinue ARVs.</td>
</tr>
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</table>
|                 |                 | • Most frequent in the first few weeks of therapy, but can occur through 18 weeks           |                     | • Treatment-naive with higher CD4 count (>250 cells/mm$^3$ in women; >400 cells/mm$^3$ in men). | • 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.  
  |                 |                 | Presentation:                                                                               |                     | • Female sex (risk is 3-fold higher in females compared with males).            | • Counsel families about signs and symptoms of HSR to ensure prompt reporting of reactions.                                           |
|                 |                 | • 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 |                     | Children:                                                      | • 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. |
|                 |                 |                                                                                             |                     | • NVP hepatotoxicity and HSR are less common in pre-pubertal children than in adults and uncommon in infants.  
  |                 |                                                                                             |                     | • High CD4 percentage is associated with increased risk of NVP toxicity.     | • 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.   |
|                 |                 |                                                                                             |                     | In the PREDICT study, the risk of NVP toxicity (rash, hepatotoxicity, hypersensitivity) was 2.65 times greater in children who had CD4 percentages ≥15% than in children who had CD4 percentages <15%. | • Do not use NVP as post-exposure prophylaxis outside of the neonatal period.             | • 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. |
|                 |                 |                                                                                             |                     |                                                                                   | • Evaluate for hypersensitivity if the patient is symptomatic.                       |                                                                                                                                          |
|                 |                 |                                                                                             |                     |                                                                                   |                                                                                       | Discontinue ARVs.                                                                                                                   |
| T-20, ETR       |                 | Onset:                                                                                       | Rare                |                                                                                   |                                                                                       | Rechallenge with T-20 or ETR is not recommended.                                                                                         |
|                 |                 | • Any time during therapy                                                                     |                     |                                                                                   |                                                                                       |                                                                                                                                          |
|                 |                 | Presentation:                                                                               |                     |                                                                                   |                                                                                       |                                                                                                                                          |
|                 |                 | • Symptoms may include rash, constitutional findings, and sometimes organ dysfunction, including hepatic failure. |                     |                                                                                   |                                                                                       |                                                                                                                                          |
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<td>HSR With or without skin involvement and excluding SJS/TEN</td>
<td>MVC</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.</td>
<td>• Discontinue all ARVs.</td>
</tr>
<tr>
<td></td>
<td>DTG</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.</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 an expert in HIV care should be consulted. **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
- CYP = cytochrome P
- ddI = didanosine
- DRESS = drug rash with eosinophilia and systemic symptoms
- DRV = darunavir
- DTG = dolutegravir
- EFV = efavirenz
- EM = erythema multiforme
- ETR = etravirine
- FPV = fosamprenavir
- FTY = fomivirsen
- 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
- T-20 = enfuvirtide
- TDF = tenofovir disoproxil fumarate
- TEN = toxic epidermal necrolysis
- TPV = tipranavir
- ZDV = zidovudine

### References


