Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

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### Table 15. Antiretroviral-Therapy-Associated Adverse Effects and Management Recommendations—Rash and Hypersensitivity Reactions  
*(Last updated May 22, 2018; last reviewed May 22, 2018)*

<table>
<thead>
<tr>
<th>Adverse Effects</th>
<th>Associated ARVs</th>
<th>Onset/Clinical Manifestations</th>
<th>Estimated Frequency</th>
<th>Risk Factors</th>
<th>Prevention/Monitoring</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. |  
- Continue the agent as tolerated by the patient.  
- Ensure patient is injecting as per instructions.  
- Rotate injection sites. |
## 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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| SJS/TEN/EM Major | Many ARVs, especially NNRTIs (see Estimated Frequency column) | Onset:  
- First few days to weeks after starting new ARV(s)  
- 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 (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. |
| DRESS | EFV, ETR, NVP, RAL, RPV, DRV | Onset:  
- 1–8 weeks after starting new ARV(s)  
- 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 from a patient presenting with suggestive symptoms. | 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. |
### Table 15. Antiretroviral-Therapy-Associated Adverse Effects and Management Recommendations—Rash and Hypersensitivity Reactions (Last updated May 22, 2018; last reviewed May 22, 2018) (page 3 of 5)

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<tr>
<td>HSR</td>
<td>ABC</td>
<td>Onset</td>
<td>With or without skin involvement and excluding SJS/TEN</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 contraindicated.</td>
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<td>With First Use:</td>
<td>Within first 6 weeks</td>
<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>With Reintroduction:</td>
<td>Within hours</td>
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<td>Most symptoms resolve within 48 hours after discontinuation of ABC.</td>
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<td>Presentation:</td>
<td>Symptoms include high fever, diffuse skin rash, malaise, nausea, headache, myalgia, arthralgia, diarrhea, vomiting, abdominal pain, pharyngitis, and respiratory symptoms (e.g., dyspnea).</td>
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<td></td>
<td>Do not rechallenge with ABC even if the patient is HLA-B*5701-negative.</td>
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<td>Symptoms worsen to include hypotension and vascular collapse with continuation of ABC. With rechallenge, symptoms can mimic anaphylaxis.</td>
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<tr>
<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>
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<td>• Most frequent in the first few weeks of therapy, but can occur through 18 weeks</td>
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<td>• Treatment-naive with higher CD4 count (&gt;250 cells/mm² in women; &gt;400 cells/mm² in men).</td>
<td>• 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.</td>
<td>Consider other causes for hepatitis and discontinue all hepatotoxic medications.</td>
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<td>Presentation:</td>
<td></td>
<td>• Female sex (risk is 3-fold higher in females compared with males).</td>
<td>• Counsel families about signs and symptoms of HSR to ensure prompt reporting of reactions.</td>
<td>Provide supportive care as indicated and monitor the patient closely.</td>
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<td></td>
<td>• 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</td>
<td></td>
<td>• NVP hepatotoxicity and HSR are less common in pre-pubertal children than in adults and uncommon in infants.</td>
<td>• 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.</td>
<td>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>High CD4 percentage is associated with increased risk of NVP toxicity. 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 &lt;15%.</td>
<td></td>
<td>• High CD4 percentage is associated with increased risk of NVP toxicity.</td>
<td>• Avoid NVP use in women with CD4 counts &gt;250 cells/mm² and in men with CD4 counts &gt;400 cells/mm² unless benefits outweigh risks.</td>
<td>Do not use NVP as post-exposure prophylaxis outside of the neonatal period.</td>
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<td>Children:</td>
<td>• Do not use NVP as post-exposure prophylaxis outside of the neonatal period.</td>
<td>• Evaluate for hypersensitivity if the patient is symptomatic.</td>
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<td></td>
<td>• NVP hepatotoxicity and HSR are less common in pre-pubertal children than in adults and uncommon in infants.</td>
<td>• Evaluate for hypersensitivity if the patient is symptomatic.</td>
<td>Rechallenge with T-20 or ETR is not recommended.</td>
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**Table 15. Antiretroviral-Therapy-Associated Adverse Effects and Management Recommendations—Rash and Hypersensitivity Reactions** (Last updated May 22, 2018; last reviewed May 22, 2018) (page 4 of 5)
Table 15l. Antiretroviral-Therapy-Associated Adverse Effects and Management Recommendations—Rash and Hypersensitivity Reactions (Last updated May 22, 2018; last reviewed May 22, 2018) (page 5 of 5)

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<tr>
<td>HSR</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>With or without skin involvement and excluding SJS/TEN</td>
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<td></td>
<td></td>
<td>• Obtain AST and ALT in patients with rash or other symptoms of hypersensitivity.</td>
<td>• Rechallenge with MVC is not recommended.</td>
</tr>
<tr>
<td>DTG</td>
<td>Rash with hepatic dysfunction</td>
<td>Rare</td>
<td>Unknown</td>
<td></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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<td></td>
<td>• Rechallenge with DTG is contraindicated</td>
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</tbody>
</table>

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
- **FTC** = emtricitabine
- **HLA** = human leukocyte antigen
- **HSR** = hypersensitivity reaction
- **IDV** = indinavir
- **IV** = intravenous
- **IVIG** = intravenous immune globulin
- **LATV** = 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**


