Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

Downloaded from https://aidsinfo.nih.gov/guidelines on 1/15/2019

Visit the AIDStinfo website to access the most up-to-date guideline.

Register for e-mail notification of guideline updates at https://aidsinfo.nih.gov/e-news.
<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>
<th>Management</th>
</tr>
</thead>
</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).  
- 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. |
| 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 | | | |
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 2 of 5)

<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>
<th>Management</th>
</tr>
</thead>
<tbody>
<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). a • 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>
</tr>
</tbody>
</table>

* a Utilize once-daily lead-in dosing (see NVP section).
<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>
<th>Management</th>
</tr>
</thead>
<tbody>
<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 contraindicated.</td>
<td>Discontinue ARVs and investigate for other causes of the symptoms (e.g., a concurrent viral illness).</td>
</tr>
<tr>
<td></td>
<td></td>
<td>With First Use:</td>
<td></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>
</tr>
<tr>
<td></td>
<td></td>
<td>Within first 6 weeks</td>
<td></td>
<td></td>
<td></td>
<td>Most symptoms resolve within 48 hours after discontinuation of ABC.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>With Reintroduction:</td>
<td></td>
<td></td>
<td></td>
<td>Do not rechallenge with ABC even if the patient is HLA-B*5701-negative.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Within hours</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Presentation:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></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>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Symptoms worsen to include hypotension and vascular collapse with continuation of ABC. With rechallenge, symptoms can mimic anaphylaxis.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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 3 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 4 of 5)

<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>
<th>Management</th>
</tr>
</thead>
<tbody>
<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></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Most frequent in the first few weeks of therapy, but can occur through 18 weeks</td>
<td></td>
<td>• Treatment-naive with higher CD4 count (&gt;250 cells/mm³ in women; &gt;400 cells/mm³ 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></td>
</tr>
<tr>
<td></td>
<td></td>
<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></td>
</tr>
<tr>
<td></td>
<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>Children:</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></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• NVP hepatotoxicity and HSR are less common in pre-pubertal children than in adults and uncommon in infants.</td>
<td>• 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.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• High CD4 percentage is associated with increased risk of NVP toxicity.</td>
<td>• Do not use NVP as post-exposure prophylaxis outside of the neonatal period.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>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>• Evaluate for hypersensitivity if the patient is symptomatic.</td>
<td></td>
</tr>
<tr>
<td>T-20, ETR</td>
<td>Rare</td>
<td>Unknown</td>
<td></td>
<td>Discontinue ARVs.</td>
<td>Rechallenge with T-20 or ETR is not recommended.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Evaluate for hypersensitivity if the patient is symptomatic.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></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>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 15I. 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)

<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>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<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>
</tr>
</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; ddl = 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; 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**


Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

Downloaded from [https://aidsinfo.nih.gov/guidelines](https://aidsinfo.nih.gov/guidelines) on 1/15/2019


