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) (page 1 of 5)

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<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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<th>Management</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 |
|                 |                 | 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, Arthritis, 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  
Unknown  
- Children and Adults:  
- >90%  
- 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.
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<td>SJS/TEN/EM Major</td>
<td>Many ARVs, especially NNRTIs (see Estimated Frequency column)</td>
<td>Onset: • First few days to weeks <strong>after starting new ARV(s)</strong> 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.</td>
<td>Infrequent: • NVP (0.3%) • EFV (0.1%) • ETR (&lt;0.1%) Case Reports: • FPV • ABC • DRV • ZDV • ddI • IDV • LPV/r • ATV • RAL</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>DRESS</td>
<td>EFV, ETR, NVP, RAL, RPV, DRV</td>
<td>Onset: • 1–8 weeks <strong>after starting new ARV(s)</strong> Presentation: • Fever • Lymphadenopathy • Facial swelling • Morbilliform to polymorphous rash • Peripheral eosinophilia • Atypical circulating lymphocytes • Internal organ involvement (particularly liver and/or renal)</td>
<td>Rare Unknown</td>
<td></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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### 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)

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<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. • HSR risk is higher in those of white race compared to those of black or East Asian race.</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. • When starting ABC, counsel patients and families about the signs and symptoms of HSR to ensure prompt reporting of reactions.</td>
<td>• 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.</td>
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**With or without skin involvement and excluding SJS/TEN**

- **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, and respiratory symptoms (e.g., dyspnea).
  - Symptoms worsen to include hypotension and vascular collapse with continuation of ABC. With rechallenge, symptoms can mimic anaphylaxis.
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| HSR With or without skin involvement and excluding SJS/TEN | NVP | Onset:  
  • Most frequent in the first few weeks of therapy, but can occur through 18 weeks  
Presentation:  
  • 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 | 4% (2.5% to 11%) | Adults:  
  • Treatment-naive with higher CD4 count (>250 cells/mm³ in women; >400 cells/mm³ in men).  
  • Female sex (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 and uncommon in infants.  
  • 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 <15%. | When Starting NVP or Restarting After Interruptions >14 Days:  
  • 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.  
  • 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 >250 cells/mm³ and in men with CD4 counts >400 cells/mm³ unless benefits outweigh risks.  
  • Do not use NVP as post-exposure prophylaxis outside of the neonatal period.  
  • Discontinue ARVs.  
  • Consider other causes for hepatitis and discontinue all hepatotoxic medications.  
  • Provide supportive care as indicated and monitor the patient closely. | Discontinue ARVs.  
  • Evaluate for hypersensitivity if the patient is symptomatic.  
  • 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. |
| T-20, ETR | Onset:  
  • Any time during therapy  
Presentation:  
  • Symptoms may include rash, constitutional findings, and sometimes organ dysfunction, including hepatic failure. | Rare | Unknown | Rechallenge with T-20 or ETR is not recommended. |
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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) (page 5 of 5)

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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
- 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**


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