Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

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<th>Associated ARVs</th>
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<tr>
<td><strong>Rash</strong></td>
<td>Any ARV can cause rash</td>
<td>Onset: &lt;br&gt; - First few days to weeks after starting new ARV(s)</td>
<td>Common (&gt;10%. Adults and/or Children): &lt;br&gt; - NVP &lt;br&gt; - EFV &lt;br&gt; - ETR &lt;br&gt; - FPV &lt;br&gt; - FTC</td>
<td>• Sulfonamide allergy is a risk factor for rash with PIs containing a sulfonamide moiety (FPV, DRV, and TPV) &lt;br&gt; • Polymorphisms in CYP2B6 and multiple HLA loci may confer increased risk of rash with NVP</td>
<td>When Starting NVP or Restarting After Interruptions &gt;14 Days: &lt;br&gt; • Utilize once-daily lead-in dosing (see NVP section). ①</td>
<td>Mild-to-Moderate Maculopapular Rash Without Systemic or Mucosal Involvement: &lt;br&gt; • Most rashes will resolve without intervention; ARVs can be continued while monitoring.③</td>
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<td></td>
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<td>Presentation: &lt;br&gt; - Most rashes are mild-to-moderate, diffuse maculopapular eruptions</td>
<td>Less Common (5% to 10%): &lt;br&gt; - ABC &lt;br&gt; - DRV &lt;br&gt; - TPV &lt;br&gt; - TDF</td>
<td>• Routinely assess patient for rash severity, mucosal involvement, and other signs of systemic reaction.</td>
<td>Rash in Patients Receiving NVP: &lt;br&gt; • Given elevated risk of HSR, measure hepatic transaminases.</td>
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<td>Note: A rash can be the initial manifestation of systemic hypersensitivity (see SJS/TEN/EM Major and HSR sections below).</td>
<td>Unusual (2% to 4%): &lt;br&gt; - LPV/r &lt;br&gt; - RAL &lt;br&gt; - MVC &lt;br&gt; - RPV</td>
<td></td>
<td>Rash Accompanied by Systemic Symptoms (e.g., Fever, Arthralgia, Edema) and/or Rash Accompanied by Mucous Membrane Involvement (e.g., conjunctivitis):</td>
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<td><strong>T-20</strong></td>
<td></td>
<td>Onset: &lt;br&gt; - First few days to weeks after starting new ARV(s)</td>
<td>Children and Adults: &lt;br&gt; - &gt;90%</td>
<td></td>
<td>Rash in Patients Receiving NVP: &lt;br&gt; • Given elevated risk of HSR, measure hepatic transaminases.</td>
<td>Continue the agent as tolerated by the patient.</td>
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<td>Presentation: &lt;br&gt; - Local injection site reactions with pain, erythema, induration, nodules and cysts, pruritus, and ecchymosis</td>
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<td></td>
<td>If hepatic transaminases are elevated, NVP should be discontinued and not restarted (see HSR-NVP below).</td>
<td>Ensure patient is injecting as per instructions.</td>
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<td>- Often multiple reactions at the same time</td>
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<td></td>
<td>Rotate injection sites.</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)

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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 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). • 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>
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<td>DRESS</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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| 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, and respiratory symptoms (e.g., dyspnea).  
• Symptoms worsen to include hypotension and vascular collapse with continuation of ABC. With rechallenge, symptoms can mimic anaphylaxis. | 2.3% to 9% (varies by ethnicity). | • HLA-B*5701 (HSR very uncommon in people who are HLA-B*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. | • 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. |
### Table 15i. 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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| 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  
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%.  | 4% (2.5% to 11%) | 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.  
• 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 | • Evaluate for hypersensitivity if the patient is symptomatic.  
Discontinue ARVs.  
Rechallenge with T-20 or ETR is not recommended. |
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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<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.*

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