Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

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Management of Children Receiving Antiretroviral Therapy (Last updated April 27, 2017; last reviewed April 27, 2017)

In the United States, the majority of children living with HIV are receiving antiretroviral therapy (ART), making treatment-experienced children the norm. Changes in the antiretroviral (ARV) regimen and other aspects of the management of treatment-experienced children can be organized into the following categories:

1. Modifying ARV regimens in children on effective ART for simplification or improved adverse event (AE) profile;
2. Recognizing and managing ARV drug toxicity or intolerance (see Management of Medication Toxicity or Intolerance);
3. Recognizing and managing treatment failure; and
4. Considerations about interruptions in therapy.

Modifying Antiretroviral Regimens in Children with Sustained Virologic Suppression on Antiretroviral Therapy

Panel's Recommendations

- Children who have sustained virologic suppression on their current regimen should be regularly evaluated for opportunities to change to a new regimen that facilitates adherence, simplifies antiretroviral (ARV) administration, increases ARV potency, and decreases the risk of drug-associated toxicity **(AII)**.
- Past episodes of antiretroviral therapy failure, tolerability, and all prior drug resistance testing results should be considered in order to avoid choosing new ARV drugs for which archived drug resistance would limit activity **(AIII)**.

Rating of Recommendations: *A = Strong; B = Moderate; C = Optional*

Rating of Evidence: *I = One or more randomized trials in children† with clinical outcomes and/or validated endpoints; I* = One or more randomized trials in adults with clinical outcomes and/or validated laboratory endpoints with accompanying data in children† from one or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes; II = One or more well-designed, nonrandomized trials or observational cohort studies in children† with long-term outcomes; II* = One or more well-designed, nonrandomized trials or observational studies in adults with long-term clinical outcomes with accompanying data in children† from one or more similar nonrandomized trials or cohort studies with clinical outcome data; III = Expert opinion*

† Studies that include children or children/adolescents, but not studies limited to post-pubertal adolescents

Initial ARV regimens are chosen based on safety, pharmacokinetic and efficacy data for drugs available in formulations suitable for the age of the child at initiation of ART. New ARV options may become available as children grow and learn to swallow pills and as new drugs, drug formulations, and data become available. Even in the setting of sustained virologic suppression (e.g., 6–12 months) on their current regimen, changing to a new ARV regimen may be considered in order to permit use of pills instead of liquids, reduce pill burden, allow use of once-daily medications, reduce risk of AEs, and align their regimens with widely used, efficacious adult regimens.[1] Often the changes enhance adherence and improve quality of life.[2]

Several studies have addressed switching ARV regimen components in children with sustained virologic suppression. Based on the NEVEREST 2 study, young children (i.e., aged <2 years) with virologic suppression who switch from lopinavir/ritonavir (LPV/r) to nevirapine can maintain virologic suppression as well as those who continue LPV/r, provided there is good adherence and no baseline resistance to nevirapine.[3,4] In the NEVEREST 3 study, children ≥3 years of age with a history of exposure to nevirapine and with virologic suppression on LPV/r maintained virologic suppression when switched from LPV/r to efavirenz.[5,6] Similarly, in the NEVEREST 2 study, children switched to a nevirapine regimen showed better immune and growth responses than those continuing a LPV/r regimen.[3] By extrapolation, replacement of LPV/r with an equally potent protease inhibitor (PI) (e.g., darunavir, atazanavir), or an integrase inhibitor (INSTI) (e.g., elvitegravir, raltegravir, dolutegravir) would likely be effective, but that has not been directly

studied. Several small studies have demonstrated sustained virologic suppression and reassuring safety outcomes when drugs that have greater long-term toxicity risk are replaced with drugs that are thought to have less toxicity risk (e.g., replacing stavudine with tenofovir disoproxil fumarate, tenofovir alafenamide, zidovudine, or abacavir; replacing PIs with non-nucleoside reverse transcriptase inhibitors), including improved lipid profiles, in small cohorts of children.[7-11] Small studies have shown that children with virologic suppression on certain twice-daily regimens (i.e., abacavir, nevirapine) maintain virologic suppression if changed from twice daily to once daily (see Abacavir and Nevirapine drug sections) but show mixed results when switching LPV/r dosing from twice daily to once daily; therefore, once-daily LPV/r is not recommended in children aged <12 years or <30kg.[12-15]

Dual and monotherapy protease inhibitor (darunavir/ritonavir, LPV/r, atazanavir/ritonavir) and INSTI (dolutegravir) strategies in adult patients with sustained virologic suppression for the purposes of simplification or reduced toxicity have been attempted with varying success. They are being further explored, but are not currently recommended as a management strategy. Limited studies have been done in children and these strategies cannot be endorsed at this time.[16-20]

Table 14 displays examples of changes in ARV regimen components that are made for reasons of simplification, convenience and safety profile in children who have sustained virologic suppression on their current regimen. When considering such a change, it is important to ensure that a child does not have virologic treatment failure. It is also critical to consider past episodes of ART, tolerability, and all prior drug resistance testing results in order to avoid choosing new ARV drugs for which archived drug resistance would reemerge and limit activity.[21-25] The evidence supporting many of these ARV changes is indirect, extrapolated from data about drug performance in initial therapy or follow-on therapy after treatment failure. When such changes are made, careful monitoring (e.g., viral load measurement 2–4 weeks after switch to new regimen) is important to ensure that virologic suppression is maintained.

Table 14: Examples of Changes in Antiretroviral Regimen Components that Are Made for Reasons of Simplification, Convenience, and Safety Profile in Children Who Have Sustained Virologic Suppression on Their Current Regimens[a] (page 1 of 2)

ARV Drug(s)	Age	Body Size Attained	Potential ARV Regimen Change	Comment[b]
NRTIs				
ABC **Twice Daily**	≥1 year	Any	ABC once daily	See Abacavir in Appendix A: Pediatric Antiretroviral Drug Information for full discussion.
ZDV or ddI (or d4T[c])	≥1 year	N/A	ABC	Once-daily dosing (see Abacavir in Appendix A: Pediatric Antiretroviral Drug Information). Less long-term mitochondrial toxicity. TDF is a reasonable option for children unable to take ABC (HLA B5701 positive) who want to switch to a once-daily regimen.
	N/A	>35 kg	TAF or ABC	N/A
	Adolescence	Pubertal maturity (i.e., SMR IV or V)	TDF, TAF or ABC	Once-daily dosing. Less long-term mitochondrial toxicity. Coformulation with other ARV drugs can further reduce pill burden. TAF preferred over TDF for lower bone toxicity.
NNRTIs				
EFV	≥12 years	≥40 kg	ATV/r DRV/r DTG RPV	Smaller pill (DTG), higher barrier to resistance given concern for adherence challenges developing in adolescents. DRV/r may be administered once daily in children aged ≥12 years without DRV resistance mutations.

Table 14: Examples of Changes in Antiretroviral Regimen Components that Are Made for Reasons of Simplification, Convenience, and Safety Profile in Children Who Have Sustained Virologic Suppression on Their Current Regimens[a] (page 2 of 2)

ARV Drug(s)	Age	Body Size Attained	Potential ARV Regimen Change	Comment[b]
PIs				
LPV/r Twice Daily	≥1 year	≥3 kg	RAL ATV/r	Better palatability. Less adverse lipid effect. Lower pill burden. Once-daily dosing (ATV/r).
	≥3 years	N/A	ATV/r EFV RAL DTG (weighing ≥30 kg) EVG (weighing ≥25 kg)	Once-daily dosing (EFV and ATV/r). Better palatability. Less adverse lipid effect. See Efavirenz in Appendix A: Pediatric Antiretroviral Drug Information regarding concerns about dosing for children aged <3 years.
	≥12 years	≥40 kg	DRV/r ATV/r DTG RPV	Once-daily dosing possible. Lower pill burden.
Other				
Any Multi-Pill and/or Twice-Daily Regimen	Adolescence	For regimens with TDF: pubertal maturity (i.e., SMR IV or V)	Co-formulated: • TDF/FTC/EFV • TDF/FTC/EVG/COBI • TAF/FTC/EVG/COBI (weighing ≥35 kg) • TDF/FTC/RPV • TAF/FTC/RPV (weighing ≥35 kg) • ABC/3TC/DTG (weighing ≥40 kg) • TAF/FTC plus DTG	Once-daily dosing. Single pill. Alignment with adult regimens. TAF/FTC plus DTG may be more desirable because of small pill sizes even though it increases pill burden to 2 pills instead of 1. TAF-based regimens can be used with adolescents weighing ≥35 kg. Use ABC/3TC/DTG for adolescents weighing ≥40kg

[a] This list is not exhaustive in that it does not necessarily list all potential options, but instead, shows examples of what kinds of changes can be made.

[b] Comments relevant to the potential ARV change listed. Does not include all relevant information. Please refer to individual drug tables for full information.

[c] Because of concerns about long-term adverse events, d4T should be replaced with a safer drug even before sustained virologic suppression is achieved (see Stavudine in Appendix A: Pediatric Antiretroviral Drug Information).

Key to Acronyms: 3TC = lamivudine; ABC = abacavir; ARV = antiretroviral; ATV/r = atazanavir/ritonavir; COBI = cobicistat; d4T = stavudine; ddI = didanosine; DRV/r = darunavir/ritonavir; DTG = dolutegravir; EFV = efavirenz; EVG = elvitegravir; FTC = emtricitabine; LPV/r = lopinavir/ritonavir; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; RAL = raltegravir; RPV=rilpivirine; SMR= sexual maturity rating (Tanner stage); TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; ZDV = zidovudine

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