

## RECOMMENDED INITIAL PAEDIATRIC HAART REGIMENS

The preferred paediatric initial regimens are summarised in *Table 4*. Three or more ARVs (generally two NRTIs--the *NRTI backbone*--combined with either an NNRTI or a PI) should always be used in conjunction to maximise the probability of sustained virologic suppression and to minimise the possibility of the development of resistance. The use of zidovudine (AZT)/lamivudine (3TC)/abacavir (ABC) as a first-line therapy is now considered a secondary alternative due to recent data from a clinical trial in HIV-infected adults (ACTG 5095a) demonstrating a significantly higher failure rate in individuals receiving this regimen than in individuals receiving similar efavirenz (EFV)-based regimens.

Preferred dual NRTI backbones include AZT plus 3TC; AZT plus didanosine (ddI); or stavudine (d4T) plus 3TC. AZT penetrates the blood brain barrier and is therefore ideally suited for infancy given the risk of HIV encephalopathy and developmental delay in this age group. d4T can be substituted for AZT if the child is anaemic or experiences AZT-related toxicity. 3TC is generally preferred over ddI for pairing with AZT and d4T because 3TC is highly potent, generally well-tolerated, and available in simple dosing formulations. EFV is not recommended in children age three years or younger or weighing less than twenty-five pounds due to the lack of dosing information and an appropriate formulation.

HAART regimens must be based on sound virologic and pharmacologic principles but must also be acceptable to the individual patient. Thus, the design of the HAART regimen is influenced by considerations of drug potency, side effect profiles, laboratory monitoring requirements, potential for maintenance of future treatment options, anticipated patient adherence, co-existent conditions, concomitant medications, availability, and cost. The potential for ARV resistance in infants infected despite ARV PMTCT prophylaxis should also be considered in the design of the HAART regimen; this issue is discussed in more detail in the section that immediately follows.

ARVs can be given to children in liquid formulations or in pills. Drug doses must be continually adjusted as the child grows to avoid under-dosing, which could lead to the development of ARV resistance. Regimens should consider the timing and interval between doses to maximise adherence. Combination formulations of ARVs are not readily available for infants and children. Nevertheless, until appropriate paediatric formulations can be made more widely available, splitting adult-dose solid formulation ARVs may be the only way a severely ill child can receive appropriate ART when no alternatives are available.

Currently available paediatric dosages and formulations of ARVs are presented in *Appendix B*, as well as significant adverse effects and toxicities associated with these ARVs.

### ***Risk of ARV resistance in Infants Who Become Infected Despite PMTCT Prophylaxis***

Infants who become infected with HIV despite antiretroviral PMTCT prophylaxis may be infected with drug-resistant virus. This is most likely to occur with PMTCT regimens using ARVs for which a single point mutation can confer drug resistance, such as NVP or 3TC; resistance is less likely to develop to ARVs for which prolonged exposure and multiple mutations are associated with resistance, such as AZT.

Hence, infants who receive SD NVP (with or without other ARVs) and become infected with HIV despite this intervention are at risk for harbouring a strain of HIV that is resistant to NVP (and by extension, to other NNRTIs, since cross-resistance in the NNRTI class is very common). This phenomenon has been documented in several clinical trials, with a range of 8 to 52% of NVP-exposed infants demonstrating NVP resistance when tested within several weeks of birth. The risk appears to be elevated in infants whose mothers also received SD NVP during labour. In theory, the development of NVP resistance in this fashion could compromise the infant's response to future NNRTI-based HAART regimens; clinical trials are underway that will hopefully answer this important question. Until more data become available, clinicians managing HIV-infected infants who were exposed to SD NVP may consider favouring PI-based HAART regimens over NNRTI-based regimens. However, if a PI-based regimen is not readily

available or is impractical for other reasons, NNRTI-based HAART can and should be used for these infants.

Variable patterns of resistance to other ARVs such as AZT and 3TC in infants exposed to these agents have also been documented. In PACTG 076, where mothers received AZT starting at 14-34 weeks gestation and infants received 6 weeks of AZT, no AZT resistance was observed in infected infants; however, in PACTG 185, where the PACTG 076 AZT regimen was given but the women were sicker at entry, 30% of infected infants had AZT resistance. In a Thai study of short-course AZT, 20% of infants infected despite prophylaxis had AZT-resistant virus. In a study in France in which 3TC was added to AZT after 32 weeks gestation and the infants received 6 weeks of AZT/3TC, 3TC resistance was observed in 2 of 5 infected infants (40%); AZT resistance was seen in 2/5 infected infants as well. In the SAINT study, where AZT/3TC was administered during labour and post-partum, no AZT or 3TC resistance was observed in infected infants. As is the case with NVP, the clinical implications remain unclear; hence, exposure to PMTCT regimens that include AZT or 3TC should not preclude the inclusion of these agents in future HAART regimens for HIV-infected infants.

**Table 4: Recommended Initial HAART Regimens for HIV-Infected Children<sup>1</sup>**

<b>Non-Nucleoside Reverse Transcriptase Inhibitor (NNRTI)-Based Regimens</b>	
Strongly Recommended:	Age >3 years: 2 NRTIs <sup>a</sup> + EFV <sup>b</sup> (with or without nelfinavir (NFV)) Age <3 years or who cannot swallow capsules: 2 NRTIs <sup>a</sup> + NVP <sup>b</sup>
Alternative Recommendation:	2 NRTIs <sup>a</sup> + NVP <sup>b</sup> (age >3 years)
<b>Protease Inhibitor (PI)-Based Regimens</b>	
Strongly Recommended:	2 NRTIs <sup>a</sup> + LPV (lopinavir)/r (Kaletra <sup>®</sup> ) or NFV or ritonavir (RTV)
Alternative Recommendation:	2 NRTIs <sup>a</sup> + indinavir (IDV) or amprenavir (APV) <sup>c</sup>
<b>Triple Nucleoside Reverse Transcriptase Inhibitor (NRTI) Regimens</b>	
Strongly Recommended:	None
Alternative Recommendation:	AZT + 3TC + ABC
<b>Regimens Not Recommended</b>	
	Monotherapy <sup>d</sup>
	Certain 2 NRTI <sup>a</sup> combinations
	2 NRTIs <sup>a</sup> + saquinavir (SQV) as sole PI <sup>d</sup>
<b>Insufficient Data to Recommend</b>	
	2 NRTIs <sup>a</sup> + delavirdine (DLV)
	Dual PIs with the exception of LPV/r <sup>e</sup>
	1 NRTI + 1 NNRTI + 1 PI <sup>f</sup>
	Regimens that contain tenofovir (TDF), atazanavir (ATV), emtricitabine (FTC), fos-amprenavir, or enfuvirtide

<sup>a</sup> Dual NRTI combination recommendations:

- Strongly Recommended: AZT + ddi + 3TC; or d4T + 3TC
- Alternative Choices: ABC + AZT or 3TC; or ddi + 3TC
- Use in Special Circumstances: d4T + ddi; or zalcitabine (ddC) + AZT
- Insufficient Data: TDF- or FTC-containing regimens
- Not Recommended: ddC + ddi, d4T, or 3TC; or AZT + d4T

<sup>b</sup> EFV is currently available only in capsule form, although a liquid formulation is currently under study to determine appropriate dosage in HIV-infected children age three years or younger; NVP would be the preferred NNRTI for children age three years or younger or who require a liquid formulation.

<sup>c</sup> APV should not be administered to children age four years or younger due to the propylene glycol and vitamin E content of the oral liquid preparation and lack of pharmacokinetic data in this age group.

<sup>d</sup> Except for AZT chemoprophylaxis administered to HIV-exposed infants during the first six weeks of life to prevent perinatal HIV transmission; if an infant is confirmed as HIV-infected while receiving AZT prophylaxis, therapy should either be discontinued or changed to a combination ARV drug regimen.

<sup>e</sup> With the exception of LPV/r, data on the pharmacokinetics and safety of dual PI combinations (e.g. low-dose RTV pharmacologic boosting of SQV, IDV, APV, or NFV) are limited, use of dual PIs as a component of initial therapy is not recommended, although such regimens may have utility as secondary treatment regimens for children who have failed initial therapy. SQV soft and hard gel capsules require low-dose RTV-boosting to achieve adequate levels in children, but pharmacokinetic data on appropriate dosing are not yet available.

<sup>f</sup> With the exception of EFV + NFV + one or two NRTIs, which has been studied in HIV-infected children and shown to have virologic and immunologic efficacy in a clinical trial.

## ***SPECIAL CONSIDERATIONS FOR PATIENTS WITH TB***

Special considerations around antiretroviral therapy must be made for the child co-infected with HIV and TB:

- ***Selection of the Initial HAART Regimen:*** NVP is generally avoided due to significant interactions with rifamycin. If EFV- or PI-based regimens are not an option, administration of the triple-NRTI regimen AZT plus 3TC plus ABC should be considered.
- ***Timing of HAART Initiation:*** The optimal time to initiate HAART in patients with TB is unclear and should be considered on a case-by-case basis. Clinical experience in Jamaica suggests that survival is improved in co-infected children who receive both HAART and TB treatment. However, it may be advisable to delay the initiation of HAART for two to eight weeks following the initiation of anti-TB medications in order to minimise pill burden, drug-drug interactions, overlapping toxicities, and the risk of immune reconstitution syndrome (IRS).<sup>\*</sup> Hence, deferral of HAART initiation until after the induction phase of TB therapy may be advisable for those children without clinical or immunological evidence of advanced HIV disease.

## ***CLINICAL MONITORING AND FOLLOW-UP***

The goals of therapy are to achieve and to maintain an undetectable HIV viral load. This prevents disease progression, optimises recovery of the immune system, and prevents antiretroviral drug resistance. An effective HAART regimen should generally result in an undetectable (e.g. less than 50 copies/mL) HIV viral load within six months of therapy initiation. Suboptimal adherence is the most common reason for failure of the initial HAART regimen. Adherence should therefore be monitored closely following therapy initiation using pill counts, pharmacy prescription refill logs, and patient/caregiver self-reports. Failure to achieve an undetectable viral load following initiation of HAART should prompt evaluation of adherence and potential drug resistance. Common reasons for suboptimal adherence include drug side effects, dosing difficulties, and inconvenience of administration.

If an undetectable HIV viral load is achieved, a significant rise in the CD4+ T cell count generally occurs, signifying partial reconstitution of the immune system. However, the degree of rise of the CD4+ T cell count can be quite variable, and some patients may not experience a significant rise in the CD4+ T cell count despite a dramatic reduction in viraemia. The optimal management of patients with this *discordant response* remains unclear, but should be based in part on consideration of clinical response to therapy. Consultation with an expert in paediatric HIV management is also recommended.

Clinical markers that suggest a positive response to HAART include:

- reduced hospitalisations;
- increased appetite, weight, and height (in children with failure to thrive);
- improved brain growth, neurodevelopment, affect, and head circumference (in those with developmental delay and/or encephalopathy); and
- reduced morbidity with reduced OIs and minor co-morbid illnesses (e.g. papular prurigo, otitis media, oral thrush, upper respiratory tract infections).

## ***TREATMENT TOXICITY***

While adverse effects from HAART are common, they can usually be managed symptomatically while continuing the HAART regimen without interruption, as most adverse effects associated with ARVs resolve within one to three months of therapy initiation. If the adverse effect is severe enough to require modification of the regimen, substitution of the offending drug with another ARV is a reasonable option

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<sup>\*</sup>See the introduction to *Chapter V: Recommendations for the Treatment of Opportunistic Infections among Adults and Adolescents* for a review of the pathophysiology and clinical presentation of IRS.

if it can be reasonably deduced which agent is responsible for the side effect in question. *Table 5* presents options for drug substitution in the event of selected common adverse reactions. Consultation with an expert HIV clinician is strongly recommended when a regimen change is necessary.

**Table 5: Common Adverse Drug Reactions Associated with First-Line HAART Regimens and Recommended Drug Substitutions<sup>2</sup>**

REGIMEN	TOXICITY	DRUG SUBSTITUTION
d4T/3TC/NVP	<ul style="list-style-type: none"> <li>d4T-related neuropathy or pancreatitis</li> <li>d4T-related lipoatrophy</li> <li>NVP-related severe hepatotoxicity</li> <li>NVP-related severe rash (but not life-threatening)</li> <li>NVP-related life-threatening rash (e.g. Stevens-Johnson syndrome)</li> </ul>	Switch d4T → AZT  Switch d4T → ABC <sup>†</sup> Switch NVP → EFV <sup>‡</sup>  Switch NVP → EFV  Switch NVP → PI <sup>§</sup>
AZT/3TC/NVP	<ul style="list-style-type: none"> <li>AZT-related persistent GI intolerance or severe haematological toxicity</li> <li>NVP-related severe hepatotoxicity</li> <li>NVP-related severe rash (but not life-threatening)</li> <li>NVP-related life-threatening rash (e.g. Stevens-Johnson syndrome)</li> </ul>	Switch AZT → d4T  Switch NVP → EFV  Switch NVP → EFV  Switch NVP → PI
d4T/3TC/EFV	<ul style="list-style-type: none"> <li>d4T-related neuropathy or pancreatitis</li> <li>d4T-related lipoatrophy</li> <li>EFV-related persistent CNS toxicity</li> </ul>	Switch d4T → AZT  Switch d4T → ABC Switch EFV → NVP
AZT/3TC/EFV	<ul style="list-style-type: none"> <li>AZT-related persistent GI intolerance or severe haematological toxicity</li> <li>EFV-related persistent CNS toxicity</li> </ul>	Switch AZT → d4T  Switch EFV → NVP

Occasionally, severe HAART-related toxicity requires discontinuation of all ARV agents. In such circumstances, it is best to discontinue all medications simultaneously, because continuation of therapy with only one or two ARV agents is associated with the development of drug resistance.\*\* HAART should be withheld until the patient recovers, at which time re-initiation of therapy with a different regimen can be considered in consultation with an HIV expert.

<sup>†</sup>Switching off d4T appears to reduce, and in some cases reverse, lipoatrophy, though very slowly. TDF and ABC represent the best alternatives to d4T in this setting, but their availability in the Caribbean is limited, and TDF cannot be recommended for paediatric use given insufficient data. ddI and AZT are reasonable alternatives where ABC is not available.

<sup>‡</sup>Except in pregnancy. If the child is a teenager of child-bearing age who is pregnant or at risk for becoming pregnant, substitute a PI (preferred) or ABC.

<sup>§</sup>Recommended PIs include LPV/r or NFV or SQV/r.

\*\*If the HAART regimen being discontinued contains an NNRTI (e.g. NVP or EFV), some expert clinicians would recommend discontinuing the NNRTI three to seven days prior to discontinuing the NRTIs, owing to the prolonged plasma half-life of NNRTIs.

## ***TREATMENT FAILURE***

Treatment failure refers to the absence of a sustained favourable response to HAART. Treatment failure can be suspected on the basis of clinical grounds, but confirmation of failure with laboratory testing is strongly recommended before changing a patient's HAART regimen. Consultation with an expert HIV clinician is also highly recommended if treatment failure is suspected on the basis of clinical, immunologic, or virologic criteria. Efforts should be made to confirm suspected treatment failure as rapidly as possible to prevent HIV disease progression and the development of further resistance to ARV agents. Laboratory testing can be useful both to establish treatment failure and in guiding second-line treatment options.

In the event of treatment failure, re-assessment of adherence is indicated. After adherence issues have been adequately addressed, a change in the HAART regimen to second-line therapy is usually warranted, as detailed later in this section.

### ***Treatment Failure: Virologic Definition***

With successful initial HAART, the HIV viral load is expected to decline by at least tenfold (one  $\log_{10}$ ) every two to eight weeks, and should be below the limit of detection of most viral load assays within approximately six months of HAART initiation. Treatment failure can be defined by the absence of such a decline in HIV viral load following initiation of therapy (*failure to suppress*), or by virologic suppression to below the lower limit of detection followed by a subsequent sustained rise in HIV viraemia (*virologic breakthrough*). These concepts are represented graphically in *Chapter IV, Figures 3 and 4*. If HIV viral load testing confirms treatment failure, consideration of second-line therapy in consultation with an HIV expert is recommended. Efforts should be made to change the HAART regimen as soon as possible to discourage the development of drug resistance and to preserve effective treatment options. Where viral load testing is not available, treatment failure can be made on the basis of immunologic or clinical criteria, as described below.

### ***Treatment Failure: Immunologic Definition***

Because of age-related declines in absolute CD4+ T cell counts until age six years when near-adult levels are reached, it is difficult to use such counts for assessing therapy failure in younger children. However, for children age six years or older, similar CD4+ T cell count criteria to those used for adults are appropriate. CD4+ T cell percentage varies less with age and is therefore more appropriate than the absolute CD4+ T cell count for gauging treatment response in younger children. Where resources permit, confirmatory repeat CD4+ T cell testing or viral load testing is warranted for the asymptomatic child suspected of failure based on immunologic criteria alone. No data exist regarding the use of the total lymphocyte count (TLC) for the evaluation of response to HAART in children.

U.S. Pediatric Guidelines<sup>iii</sup> suggest the following criteria for immunologic failure:

- Change in CDC immunologic classification (see *Appendix C* for immunologic classification schemes);<sup>6</sup> or
- For children with CD4+ T cell percentages of <15% (e.g. those in immune category 3), a persistent decline of  $\geq 5\%$  in CD4+ T cell percentage (e.g. from 15% to 10%); or
- A rapid and substantial decrease in absolute CD4+ T cell count (e.g. >30% decline in less than six months).

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<sup>6</sup>Minimal changes in CD4+ T cell percentile that may result in change in immunologic category (e.g. from 26% to 24%, or 16% to 14%) may not be as concerning as a rapid substantial change in CD4+ T cell percentile within the same immunologic category (e.g. a drop from 35% to 25%).

WHO criteria<sup>iv</sup> for treatment failure in children include:

- Return of CD4+ T cell percentage (or for children age six years or older, of absolute CD4+ T cell count) to pre-therapy baseline or below, in absence of other concurrent infection explaining transient CD4+ T cell decrease; or
- >50% fall from peak level on therapy of CD4+ T cell percentage (or for children age six years or older, of absolute CD4+ T cell count) in absence of other concurrent infection explaining transient CD4+ T cell decrease.

***Treatment Failure: Clinical Definition***

Treatment failure should be suspected if progression of HIV disease continues following HAART initiation or if no clinical improvement occurs in three months following therapy initiation. Clinicians must be careful to distinguish suspected HIV disease progression from IRS, which can also manifest with fevers, night sweats, and fatigue, but does not signify treatment failure. IRS typically resolves within a couple of months following initiation of HAART, whereas a new OI generally will not. Further discussion of IRS can be found in the introduction to *Chapter V: Recommendations for the Treatment of Opportunistic Infections among Adults and Adolescents*.

In children, important clinical signs of treatment failure include:

- lack of growth, or falling off of growth in children with an initial growth response;
- loss of neurodevelopmental milestones or development of encephalopathy;
- occurrence of new OIs or of a malignancy signifying clinical disease progression;<sup>7</sup> and
- recurrence of minor and major OIs that may be refractory to therapy, e.g. oral candidiasis.

***Management of Suspected Treatment Failure***

It should not be concluded on the basis of clinical criteria alone that a HAART regimen is failing until the child in question has had a reasonable treatment trial (e.g. receiving the regimen for at least twenty-four weeks). The HAART regimen should not be changed unless ongoing poor adherence has been ruled out for failure. Laboratory testing at six months, especially viral load testing, is strongly recommended if treatment failure is still suspected six months following the initiation of HAART. The viral load results should be confirmed, if possible, to ensure that the suggested change is needed. Laboratory results should be reviewed with an expert HIV clinician to guide management decisions. If treatment failure is confirmed, a change in HAART to a second-line regimen is generally recommended, although if a regimen has brought the viral load to low or nearly undetectable levels, intensification of the current regimen with the addition of another drug may be a reasonable alternative strategy.

Where reasonable options for second-line HAART regimens are lacking, it may be more advantageous to continue the initial HAART regimen despite a suboptimal response rather than change regimens. However, it should be recognised that this approach risks the ongoing development of ARV drug resistance, which can further compromise future treatment options.

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<sup>1</sup>*Ibid.*

<sup>2</sup>World Health Organisation. Table C: Major potential toxicities of first-line ARV regimens recommended drug substitutions in Revised WHO guidelines for scaling up antiretroviral

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<sup>7</sup>This must be distinguished from IRS, which can occur in the first three months following HAART initiation and does not signify treatment failure.

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therapy in resource-limited settings. 2004 revision. Available at:  
<[http://www.who.int/3by5/publications/documents/arv\\_guidelines/en](http://www.who.int/3by5/publications/documents/arv_guidelines/en)>.

<sup>iii</sup>NPHRC/HRSA/NIH, 2004.

<sup>iv</sup>World Health Organisation, 2003.