

SELECTION OF INDIVIDUAL AGENTS IN THE HAART REGIMEN

The nucleoside backbone of an initial regimen typically includes 3TC due to its potency, few adverse effects, and low pill burden (one pill once or twice daily) without food restrictions. 3TC is commonly paired with AZT or d4T to complete the nucleoside backbone. 3TC can also be combined with other agents such as ABC or TDF, but these agents are not as commonly available in the Caribbean. FTC can be substituted for 3TC, but this agent is not yet commonly available in the region.

The use of certain nucleoside combinations is specifically discouraged. AZT and d4T should not be combined because these agents are antagonistic *in vivo*. The combination of ddI and d4T should be avoided due to an overlapping toxicity profile that significantly raises the possibility of serious adverse events such as lactic acidosis, pancreatitis, hepatitis, or peripheral neuropathy. 3TC and FTC should not be combined since they are very similar drugs with identical resistance patterns.

Due to the risk of teratogenicity associated with EFV, NVP rather than EFV should be used in women who are pregnant or at risk of becoming pregnant. However, a high incidence of symptomatic liver toxicity (11%) has been reported in women with CD4+ T cell counts >250 cells/mm³ who initiate NVP-based therapy; NVP should therefore be used cautiously in such women, and close laboratory monitoring is recommended. Men with CD4+ T cell counts >400 cells/mm³ appear to be at increased risk for NVP-induced hepatotoxicity as well. For individuals not at risk for pregnancy, EFV may be preferred over NVP, because EFV has a generally more favourable toxicity profile and may be more potent than NVP (EFV-based HAART regimens have generally performed better than NVP-based HAART regimens in clinical trials, though a recent head-to-head trial failed to demonstrate a significant difference in efficacy between the two agents). Nevertheless, the significant teratogenic potential of EFV renders this agent unsuitable for women who are pregnant or may become pregnant while on the medication.

PI-based regimens are not as highly recommended in these guidelines for initial HAART, chiefly due to the high pill burden and refrigeration requirements for some PIs. However, because numerous clinical trials have confirmed the efficacy of PI-based HAART regimens, they can be considered as reasonable alternative initial HAART regimens. Clinical trial data most strongly support the long-term efficacy and potency of LPV/ritonavir (LPV/r). The potency of this agent is likely attributable at least in part to the inclusion of RTV, which significantly boosts the circulating plasma levels of LPV by inhibiting its metabolism. RTV will similarly boost the serum drug levels of other PIs, and many clinicians favour routinely boosting PIs with a low dose of co-administered RTV in order to improve pharmacokinetics and to simplify dosing and food requirements; see *Appendix B* for background and dosing information regarding the use of low-dose RTV to boost serum levels of other PIs. Unfortunately, RTV requires refrigeration,* making its use problematic in many parts of the Caribbean where a 'cold chain' of distribution cannot be guaranteed. SQV also requires refrigeration, but other PIs do not. Where refrigeration cannot be guaranteed and a PI-based regimen is indicated, NFV is an attractive alternative due to its relatively simple dosing and favourable toxicity profile. ATV is a new PI with a lower pill burden and higher potency than NFV but is not yet widely available in the region.

Recommendations

These guidelines therefore suggest a nucleoside backbone of AZT plus 3TC or d4T plus 3TC, combined with EFV or NVP, as the initial HAART regimen. Due to the risk of teratogenicity associated with EFV, NVP rather than EFV should be used in women who are pregnant or at risk of becoming pregnant. See *Table 6* for preferred initial regimens, along with their respective advantages and disadvantages; see *Table 7* for alternative initial HAART options. For HAART considerations in patients with co-morbid conditions (e.g. hepatitis, diabetes, or tuberculosis (TB)), see the following chapter. For ART considerations in pregnant women, see *Chapter VII: Antiretroviral Therapy in Pregnant Women and Prevention of Mother-to-Child Transmission of HIV*.

*RTV should be stored at 2° to 8°C (36° to 46°F) prior to dispensing. After dispensing, it can be stored at room temperature (defined as less than 25°C, or 77°F) as long as it is used within thirty days (Source: Norvir® (ritonavir) package insert. Abbott Park, Ill: Abbott Pharmaceuticals).

Table 6: Preferred Initial HAART Regimens

REGIMEN	ADVANTAGES	DISADVANTAGES
<ul style="list-style-type: none"> • AZT + 3TC + EFV 	<ul style="list-style-type: none"> • Simple • Highly potent • Generally well-tolerated • Less potential for toxicities associated with mitochondrial dysfunction** • Less potential for skin and liver toxicity than NVP-based regimens • May be more potent than NVP-based regimens* 	<ul style="list-style-type: none"> • Contra-indicated in women who are pregnant or may become pregnant (EFV)[†] • Potential for EFV-associated CNS side effects[‡] • Potential for AZT-associated anaemia
<ul style="list-style-type: none"> • AZT + 3TC + NVP[§] 	<ul style="list-style-type: none"> • Simple • Highly potent • Generally well-tolerated • Less potential for toxicities associated with mitochondrial dysfunction** • Not contra-indicated in pregnancy • Less potential for EFV-associated CNS side effects 	<ul style="list-style-type: none"> • Higher potential for liver, skin toxicity than EFV-based regimens^{††} • Potential for AZT-associated anaemia • May be less potent than EFV-based regimens*
<ul style="list-style-type: none"> • d4T + 3TC + EFV 	<ul style="list-style-type: none"> • Simple • Highly potent • Generally well-tolerated • Unlikely to induce or worsen anaemia • Less potential for skin and liver toxicity than NVP-based regimens • May be more potent than NVP-based regimens 	<ul style="list-style-type: none"> • Contra-indicated in women who are pregnant or may become pregnant (EFV) • Potential for EFV-associated CNS side effects • Higher potential for toxicities associated with mitochondrial dysfunction**
<ul style="list-style-type: none"> • d4T + 3TC + NVP[§] 	<ul style="list-style-type: none"> • Simple • Highly potent • Generally well-tolerated • Unlikely to induce or worsen anaemia • Not contra-indicated in pregnancy • Less potential for EFV-associated CNS side effects 	<ul style="list-style-type: none"> • Higher potential for liver, skin toxicity than EFV-based regimens^{††} • Higher potential for toxicities associated with mitochondrial dysfunction** • May be less potent than EFV-based regimens*

*EFV-based HAART regimens have generally performed better than NVP-based HAART regimens in clinical trials, though a recent head-to-head trial failed to demonstrate a significant difference in efficacy between the two agents.

[†]Severe neurological birth defects have been documented in the offspring of non-human primates exposed to EFV during pregnancy.

[‡]CNS effects commonly associated with EFV include dizziness, impaired concentration, and psychological changes; these effects typically clear after the first few weeks of therapy.

[§]NVP should be dosed at half-strength for the first two weeks of therapy, followed by escalation of the dose to full strength, in order to minimise the risk of skin and liver toxicity.

**Toxicities due to NRTI-induced mitochondrial dysfunction (lactic acidosis, peripheral neuropathy, pancreatitis, and lipodystrophy) are more commonly associated with d4T than AZT.

^{††}Risk of NVP-induced hepatotoxicity is especially elevated in women with pre-HAART CD4+ T cell counts of >250 cells/mm³ and in men with pre-HAART CD4+ T cell counts of >400 cells/mm³.

Table 7: Alternative Initial HAART Regimens

REGIMEN EXAMPLES	ADVANTAGES	DISADVANTAGES
TDF + 3TC + NNRTI⁸ <ul style="list-style-type: none"> • TDF + 3TC + EFV • TDF + 3TC + NVP 	<ul style="list-style-type: none"> • Highly potent • Low pill burden • Once-daily option with EFV may improve adherence 	<ul style="list-style-type: none"> • TDF not widely available in Caribbean • Potential for liver, skin toxicity (NVP>EFV) • Teratogenicity (EFV) • Second-line options may be limited
2 NRTIs + LPV/r <ul style="list-style-type: none"> • AZT + 3TC + LPV/r • d4T + 3TC + LPV/r 	<ul style="list-style-type: none"> • Highly potent • Less potential for liver, skin toxicity than NNRTI-based regimens 	<ul style="list-style-type: none"> • LPV/r not commonly available in the Caribbean • High pill burden • High potential for drug-drug interactions • GI side effects common (LPV/r) • Refrigeration requirement (LPV/r)
2 NRTIs + NFV <ul style="list-style-type: none"> • AZT + 3TC + NFV • d4T + 3TC + NFV 	<ul style="list-style-type: none"> • Reasonably well-tolerated • No refrigeration requirements • Fewer drug interactions than other PI-based regimens 	<ul style="list-style-type: none"> • High pill burden⁹ • Lower potency than EFV- or LPV/r-based regimens • Diarrhoea common (NFV)
2 NRTIs + ATV <ul style="list-style-type: none"> • AZT + 3TC + ATV • d4T + 3TC + ATV • TDF + 3TC + ATV 	<ul style="list-style-type: none"> • Well-tolerated • Low pill burden • No refrigeration requirements • Higher potency than NFV-based regimens • Unlike other PIs, ATV not associated with dyslipidaemia • TDF/3TC/ATV can be dosed once-daily 	<ul style="list-style-type: none"> • ATV not widely available in the Caribbean • Unclear if potency equivalent to EFV- or LPV/r-based regimens (though comparable potency likely if ATV is boosted by low-dose RTV)
3 NRTIs <ul style="list-style-type: none"> • AZT + 3TC + ABC • d4T + 3TC + ABC 	<ul style="list-style-type: none"> • Generally well-tolerated • Potentially fewer metabolic complications¹⁰ • Preserves PI and NNRTI options 	<ul style="list-style-type: none"> • Lower potency than EFV- or LPV/r-based regimens • Potential for ABC hypersensitivity

Drug Interactions

Drug interactions between PIs and NNRTIs are common, and dosing adjustments are required for certain combinations of ARV agents (see *Appendix B* for details). Drug interactions between these drugs and medications used to treat other conditions are also common (see *Appendix C*). Potential drug interactions must be investigated and appropriate modifications made prior to initiation of HAART. *Appendix D* lists drugs that should not be used in patients on HAART due to potentially severe drug-drug interactions.

⁸Do not use EFV in women who are pregnant or at risk for pregnancy.

⁹New dose formulation of NFV (625mg/tablet) reduces pill burden to two NFV tabs b.i.d (where available).

¹⁰Triple-NRTI regimens have been associated with a lower risk of dyslipidaemia, lipodystrophy, and insulin resistance than NNRTI- or PI-based regimens.

