

SECOND-LINE AND SALVAGE ANTIRETROVIRAL THERAPY

Treatment failure of the initial HAART regimen is a common, though not inevitable, event. When initial treatment fails, a second-line regimen is generally implemented. *Salvage therapy* refers to treatment regimens designed for patients who have failed two or more ARV regimens. In general, each successive HAART regimen is less likely than the previous regimen to achieve durable virologic and immunologic success. Hence, treatment regimens must be selected carefully to maximise a patient's likelihood of a robust and durable response to HAART.

HIV RESISTANCE TO ARV MEDICATIONS

Treatment failure often (though not always) occurs because a patient's strain of HIV has developed resistance to one or more of his or her ARVs. The development of resistance by HIV is similar to the way in which bacteria or mycobacteria (e.g. TB) develop resistance to antibiotics: insufficiently potent drug therapy selects for mutant strains that are resistant to the medications administered to the patient. These mutant strains then replace the wild-type strain due to their selective replication advantage in the face of drug pressure, leading to treatment failure. Resistance to ARVs most commonly develops in the setting of suboptimal adherence, but can occur even in patients who maintain very high levels of adherence to their medications. For example, a patient with poorly-controlled diarrhoea may not fully absorb his or her medications, leading to subtherapeutic drug levels in the blood, which could lead to the development of resistance.

Cross-resistance between ARV drugs within drug classes is common; for example, a strain of HIV that is resistant to NVP is very likely to be highly resistant to EFV as well, and *vice versa*. Considerations of potential cross-resistance must therefore be incorporated into the design of second-line and salvage treatment regimens.

Laboratory assays have been developed to estimate the patterns of resistance that have developed in a given patient's strain of HIV. Though imperfect, these assays have demonstrated clinical efficacy in aiding the design of second-line treatment regimens following treatment failure. Unfortunately, these assays are very expensive and not widely available in the Caribbean. However, where available, a resistance assay can provide valuable information for patients experiencing treatment failure.

Even in the absence of resistance testing, knowledge of the patterns of resistance and cross-resistance that commonly develop in patients failing specific regimens allows for reasonably accurate empiric decision-making in designing a second-line regimen. Empirically designed algorithms have been incorporated into the design of second-line treatment regimens (see *Table 6*).

A more detailed discussion of ARV resistance and resistance assays can be found in *Appendix F* of *Chapter IV*.

SECOND-LINE HAART REGIMENS

Second-line HAART regimens are indicated for patients who are forced to discontinue their initial treatment regimen as a consequence of treatment failure or severe toxicity. Consultation with an expert HIV clinician is highly recommended when designing a second-line regimen. If the initial regimen was discontinued due to toxicity without evidence of treatment failure, then the second-line regimen should involve substitution of the drug most likely to be responsible for the toxicity, as outlined in *Table 5*. For example, if a child develops a severe skin rash after starting an initial regimen of d4T plus 3TC plus NVP, a second-line regimen can be constructed using the same nucleoside backbone but with a different third agent, because it can be reasonably assumed that the NVP was responsible for the skin reaction.ⁱ

If the initial HAART regimen was discontinued due to treatment failure, however, it is likely that drug resistance to one or more ARV agents in the initial regimen has developed. The next HAART regimen must be constructed carefully to account for this potential resistance. Where available, ARV resistance testing is strongly recommended to help guide the design of the second-line regimen. If a resistance-testing assay is not available, empiric reasoning regarding the likelihood of resistance to agents in the initial regimen, as well as considerations of cross-resistance, can be used to design a second-line regimen with the highest likelihood of efficacy. Because the exact nature and extent of resistance is difficult to estimate empirically, these guidelines suggest trying to replace as many of the agents in the initial regimen as possible.

Resistance to 3TC and to NNRTIs commonly develops in patients who fail initial treatment regimens containing these agents. Hence, second-line regimens for patients who initiated an NNRTI-based regimen generally involve replacement of the NNRTI with a PI.* Conversely, initial PI-based regimens should generally be replaced with NNRTI-based regimens.

Most initial HAART regimens will also contain either AZT or d4T. Unfortunately, AZT and d4T share similar resistance patterns, and a high degree of cross-resistance between these two drugs limits the utility of replacing one of them with the other. Hence, for patients failing AZT- or d4T-containing HAART regimens, the best second-line options include a nucleoside backbone of ddI plus ABC. Unfortunately, ABC is not universally available in the Caribbean. Fortunately, AZT and d4T will often retain at least partial efficacy in a second-line regimen, because typically HIV must develop multiple resistance mutations before achieving full resistance to either of these agents. Hence, where ABC is not available, AZT or d4T may be used in second-line regimens. The use of TDF cannot be recommended due to insufficient data regarding its use in paediatric patients.

Table 6: Second-Line Regimen Recommendations for Treatment Failure

FAILED FIRST-LINE REGIMEN	SECOND-LINE REGIMEN OPTIONS [†]	COMMENTS
d4T + 3TC + EFV or d4T + 3TC + NVP	ABC + ddI + PI/r [§] or AZT + ddI + PI/r or Substitute NFV for PI/r in above options	<ul style="list-style-type: none"> • ABC not widely available; beware of ABC hypersensitivity • Potency questionable due to cross-resistance between d4T and AZT • PI/r favoured over NFV due to higher potency
AZT + 3TC + EFV or AZT + 3TC + NVP	ABC + ddI + PI/r or AZT + ddI + PI/r or ABC + ddI + AZT + PI/r or Substitute NFV for PI/r in	<ul style="list-style-type: none"> • ABC not widely available; beware of ABC hypersensitivity • Potency questionable • Higher pill burden and risk of toxicity • PI/r favoured over NFV due to higher potency

* LPV/r is the preferred PI in this circumstance given its high potency and established paediatric dosing and formulation. The use of PIs other than LPV/r and NFV is more problematic in children because of a lack of suitable paediatric drug formulations for IDV and SQV and a lack of appropriate dosing information for RTV-boosted PIs other than LPV/r. However, SQV/r maybe considered as an alternative in children who weigh 25kg or more, and can therefore receive the adult dosage.

[†] 3TC may be added to any of the above regimens. Some expert clinicians suggest continuing 3TC therapy even for patients in whom 3TC resistance is likely, due to reduced replicative capacity (*viral fitness*) induced by the signature 3TC resistance mutation.

[§] PI/r = RTV-boosted PI (LPV/r or, for children >25 kg, SQV/r)

	above options	
AZT + 3TC + ABC	ABC + ddI + (EFV or NVP) or ABC + ddI + PI/r or ABC + ddI + NFV or Substitute d4T for ABC in above options	<ul style="list-style-type: none"> • Potency questionable; ABC may still retain some activity • PI/r favoured over NFV due to higher potency • d4T + ddI combination not generally recommended due to excess toxicity
2 NRTIs + (PI or PI/r)	2 different NRTIs + (EFV or NVP) or 2 different NRTIs + PI/r	<ul style="list-style-type: none"> • See patterns above for NRTI selection • Because PI resistance develops relatively slowly, an PI/r-based second-line therapy may be effective even for patients who failed initial PI-based therapy

SALVAGE THERAPY

Following failure of two or more ARV regimens, durable virologic suppression is unlikely. However, prevention of further immunologic deterioration is possible even in the absence of full virologic suppression. Studies in adults have demonstrated that highly treatment-experienced patients, including those with demonstrably high levels of ARV resistance, generally fare better clinically if they remain on HAART than if they discontinue antiretroviral therapy altogether. Hence, while full virologic suppression may not be a realistic goal for highly treatment-experienced patients, attempts should be made to construct a regimen that will still maintain some efficacy and hopefully prevent or slow further progression of HIV disease. The design of salvage therapy regimens is exceedingly complex and should be performed in consultation with an expert HIV clinician.

ⁱSteel-Duncan JC, Pierre R, et al. NVP-associated rash in a Jamaican child with HIV/AIDS. *West Indian Med J* 2004;53(5):356–358.