

# CHAPTER IV. RECOMMENDATIONS FOR ANTIRETROVIRAL THERAPY FOR ADULTS AND ADOLESCENTS WITH HIV INFECTION

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## IV: RECOMMENDATIONS FOR ANTIRETROVIRAL THERAPY FOR ADULTS AND ADOLESCENTS WITH HIV INFECTION

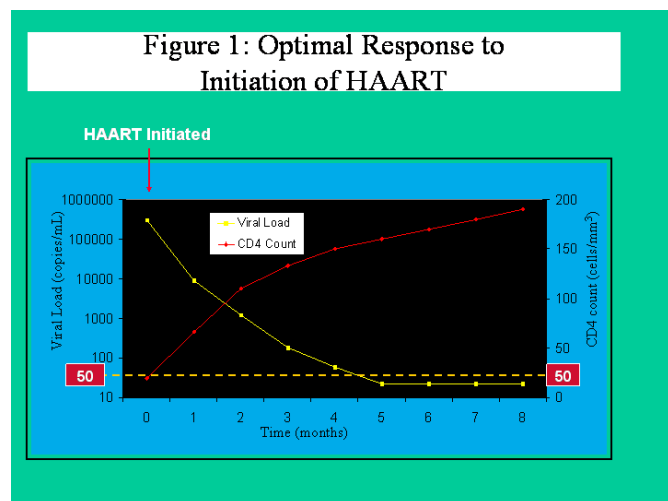
### OVERVIEW OF ANTIRETROVIRAL THERAPY (ART)

#### HIGHLY ACTIVE ANTIRETROVIRAL THERAPY (HAART)

HAART, defined as the combination of three or more antiretroviral (ARV) agents taken concurrently to suppress HIV replication,\* represents the current standard of care of antiretroviral therapy for individuals infected with HIV. This strategy evolved from the recognition that treatment of chronic HIV infection with only one or two ARV agents typically results in rapid treatment failure and the development of ARV resistance, compromising future therapeutic options.

Ultimately, the goal of HAART is the prevention of HIV-associated morbidity and mortality. This is most effectively achieved by suppressing HIV replication to a level below the limit of detection by viral load assays (generally less than 50 copies/mL). Suppression of HIV replication with HAART is typically associated with a significant rise in the CD4+ T cell count, reflecting partial reconstitution of the immune system that results in reduced HIV-related morbidity and mortality and in improved quality of life.

Hence, for HIV-infected individuals initiating ARV therapy, full suppression of virologic replication should be the goal. (See *Figure 1* for a graphic depiction of the optimal response to HAART in a patient with advanced HIV disease.) For highly treatment-experienced patients who have developed significant resistance to various ARV agents, suppression of viral replication to an undetectable level may no longer be a realistic goal. However, an appropriately designed HAART regimen for such patients will often result in stabilisation of HIV disease progression, even in the absence of full virologic suppression.



#### CLASSES AND CHARACTERISTICS OF ARVs

HAART regimens are typically constructed using agents selected from two or three drug classes. These classes are based on their mechanisms of action in suppressing HIV replication (see *Figure 2*). The three main classes include the nucleoside reverse transcriptase inhibitors (NRTIs),<sup>†</sup> non-nucleoside reverse transcriptase inhibitors (NNRTIs), and protease inhibitors (PIs). NRTIs and NNRTIs suppress HIV replication by inhibiting the action of *HIV reverse transcriptase*, while PIs inhibit the *HIV protease* enzyme. A fourth class of ARV agents has recently been introduced with enfuvirtide, a fusion inhibitor that blocks HIV cell entry. However, enfuvirtide is not available in oral form, is very expensive, and is

\*HAART can be more strictly defined as: (a) two or more NRTIs in combination with at least one PI or one NNRTI; (b) one NRTI in combination with at least one PI and at least one NNRTI; (c) a regimen containing RTV and SQV in combination with one NRTI and no NNRTIs; or (d) an ABC- or TDF-containing regimen of three or more NRTIs in the absence of both PIs and NNRTIs. (Source: US DHHS. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. 2004. Available at: <http://AIDSinfo.nih.gov/guidelines>. Accessed January 2005.)

<sup>†</sup>Tenofovir diproxil fumarate (TDF) is considered a member of the NRTI class, though technically, it is a nucleoside reverse transcriptase inhibitor because it is monophosphorylated, whereas the nucleoside reverse transcriptase inhibitors are not phosphorylated.

generally only considered for patients with very few remaining ARV options (see *Table 1* for a summary of these ARV agents).

HAART regimens typically consist of two NRTIs (the *nucleoside backbone*) combined with an NNRTI or one to two PIs. Choosing which combination to use depends on considerations of drug potency, tolerability, potential for adherence, and resistance as discussed later in this chapter.

### PRINCIPLES OF HAART: INITIAL THERAPY

Initiation of HAART represents a critical intervention for individuals infected with HIV. The potential benefits of HAART (delayed progression of HIV disease, reconstitution of the immune system) must be weighed against the potential drawbacks (medication toxicities, lifestyle changes, potential for developing drug resistance). Though some controversy remains regarding the optimal time at which HAART should be initiated (as well as the best initial treatment regimen), general guiding principles concerning these decisions can be made and are presented below. Please note that specific circumstances may warrant deviation from the guidelines for individual patients.

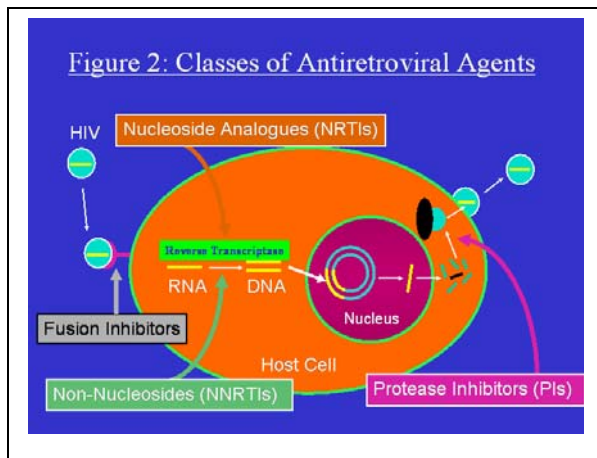
#### TIMING OF HAART INITIATION

Four key variables should be considered when deciding if HAART should be initiated for an individual infected with HIV: 1) HIV-related symptoms; 2) CD4+ T cell count; 3) HIV viral load; and 4) the patient's potential for adherence.

Patients with significant symptoms attributable to HIV infection should generally be offered HAART as soon as possible. Initiation of therapy for those individuals with no symptoms or only mild HIV-related symptoms should largely depend upon CD4+ T cell count measurements (or total lymphocyte count if CD4+ T cell count testing is not available).

Some controversy remains as to the optimal CD4+ T cell count threshold for initiation of HAART in the asymptomatic patient. When HAART first became available with the development of PIs in the late 1990s, most experts and guidelines advocated aggressive use of HAART, even for patients with relatively high CD4+ T cell counts and low HIV viral load levels. However, it was soon discovered that while HAART can suppress HIV replication to undetectable levels, HAART cannot fully eradicate the virus. Furthermore, long-term adverse effects associated with ARV agents were increasingly recognised as individuals continued therapy for several years. These factors have prompted most experts to favour a less aggressive approach to HAART than was advocated in the past.

Several observational cohort studies of HIV-infected patients have suggested that patients who initiate HAART before their CD4+ T cell count falls to  $<200$  cells/mm<sup>3</sup> have a higher likelihood of durable virologic suppression, a lower likelihood of progression of HIV disease, and more robust immune reconstitution as compared to patients who initiate HAART after their CD4+ T cell counts have dropped to  $<200$  cells/mm<sup>3</sup>. While these studies suggest a benefit associated with initiation of therapy at CD4+ T cell counts  $>200$  cells/mm<sup>3</sup>, studies have not consistently suggested a significant benefit of initiation of HAART at higher CD4+ T cell counts ( $>350$  cells/mm<sup>3</sup>). Earlier studies in the pre-HAART era documented a relatively high rate of progression to AIDS among patients with viral loads of  $<55,000$  copies/mm<sup>3</sup>, regardless of their CD4+ T cell count. More recent studies have also suggested that a high baseline viral load ( $>100,000$  copies/mm<sup>3</sup>) at the time HAART is initiated may be associated with less



favourable clinical outcomes, though this phenomenon has not been seen consistently in studies of more potent regimens that include EFV or LPV/r.

**These guidelines therefore recommend initiation of treatment (HAART) for patients with significant or AIDS-defining symptoms, regardless of CD4+ T cell count or HIV viral load. Initiation of HAART is also recommended for asymptomatic patients with a CD4+ T cell count of <200 cells/mm<sup>3</sup>. For asymptomatic patients or patients with minor symptoms who have a CD4+ T cell count between 200 and 350 cells/mm<sup>3</sup>, HAART should generally be offered, recognising that a better response to HAART is likely if treatment is initiated before the CD4+ T cell count falls to <200 cells/mm<sup>3</sup>. Any evidence of HIV disease progression should warrant prompt consideration of treatment initiation regardless of CD4 count. Finally, for patients who are asymptomatic and have a high CD4+ T cell count (>350 cells/mm<sup>3</sup>) or a high total lymphocyte count (>1,200 cells/mm<sup>3</sup>), HAART may generally be deferred. Because the response to HAART correlates strongly with adherence, the patient's potential for adherence should be assessed carefully, and attempts should be made to address and correct potential obstacles to adherence prior to initiation of therapy.\***

A patient's baseline HIV viral load level is not as important as symptoms or CD4+ T cell count in deciding when to initiate therapy. However, if available, this information can be used to estimate the anticipated rate of disease progression: in the absence of therapy, higher viral loads typically correlate with faster rates of disease progression and CD4+ T cell count decline. Furthermore, some studies suggest that initiation of HAART at lower baseline viral loads is associated with a better clinical response to treatment than in patients who initiate HAART at higher baseline viral loads. Some experts and clinical guidelines therefore recommend initiation of HAART for patients with high viral loads (e.g. >50,000 to 100,000 copies/mL), even if the CD4+ T cell count is >350 cells/mm<sup>3</sup>. Other experts might recommend simply following the CD4+ T cell count more carefully in patients with high baseline viral loads to ensure that treatment is initiated before the CD4+ T cell count falls to <200 cells/mm<sup>3</sup>.

*Table 1* summarises these guidelines for initiation of HAART. In regions where CD4+ T cell count testing is not available, the total lymphocyte count (TLC) can be used as a marker of immunosuppression in symptomatic patients. Because the TLC does not accurately reflect HIV-related immunosuppression in asymptomatic patients, recommendations for initiation of HAART for asymptomatic patients cannot be made on the basis of the TLC.

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\*Adherence is discussed in more detail later in this chapter, as well as in *Chapter 1: Comprehensive Management of Persons with HIV Infection*.

**Table 1: General Recommendations for Initiation of HAART for HIV-Infected Adults and Adolescents.** Please refer to text for additional guidance and considerations.

<b>IF CD4+ T CELL COUNT TESTING IS AVAILABLE</b>			
<b>Symptoms of HIV</b>	<b>CD4+ T Cell Count (cells/mm<sup>3</sup>)</b>	<b>Viral Load (copies/mL) (if available)</b>	<b>Recommendation</b>
Severe Symptoms (WHO Stage III-IV)	Any	Any	Treat
Asymptomatic or minor symptoms (WHO Stage I-II)	<200	Any	Treat
Asymptomatic or minor symptoms (WHO Stage I-II)	200-350	Any	Offer treatment with goal of starting therapy before CD4 count falls below 200 ( <i>see text</i> )
Asymptomatic or minor symptoms (WHO Stage I-II)	>350	>100,000	Treatment decision controversial; monitor CD4+ T cell count closely ( <i>see text</i> )
Asymptomatic or minor symptoms (WHO Stage I-II)	>350	<100,000	Treatment not recommended

<b>IF CD4+ T CELL COUNT TESTING IS UNAVAILABLE</b>		
<b>Symptoms of HIV Infection</b>	<b>Total Lymphocyte Count (cells/mm<sup>3</sup>)</b>	<b>Recommendation</b>
Severe Symptoms (WHO Stage III-IV)	Any	Treat
Minor symptoms (WHO Stage II)	<1200	Treat
Minor symptoms (WHO Stage II)	>1200	Consider treatment
Asymptomatic (WHO Stage I)	Any	Treatment not recommended

## **ADHERENCE**

Studies have also consistently demonstrated that very high levels of adherence are required to maintain a robust response to HAART with durable virologic suppression. In fact, recent data suggest that adherence is a more important predictor of response to HAART than the baseline CD4+ T cell count or HIV viral load. Furthermore, suboptimal adherence often rapidly leads to the development of ARV resistance, limiting treatment options. Hence, adherence issues must be explored thoroughly before initiation of HAART, and potential obstacles to adherence should be addressed and corrected if possible. The selection of the HAART regimen itself should take into account patient preferences that favour adherence. Research has identified several factors associated with adherence, some of which are listed in [Table 2](#).

**Table 2: Selected Factors that May Influence Adherence**

ASSOCIATED WITH POOR ADHERENCE	ASSOCIATED WITH BETTER ADHERENCE
Active alcohol or substance abuse	Directly observed therapy (DOT)
Regimen complexity	Once- or twice-daily regimens
Depression	Not living alone
Lack of perceived efficacy of HAART	Belief in efficacy of HAART
Lack of symptomatic disease	History of OI or advanced HIV disease
Concern over side effects	Belief in own ability to adhere to regimen
Work outside the home for pay	Belief that non-adherence will lead to viral resistance
Lack of proper instructions to patient	Dependence on a significant other for support

A multidisciplinary approach can be useful for exploring potential barriers to adherence with individual patients. Ideally, any potential barriers to adherence should be corrected prior to initiation of HAART. However, many potential barriers to adherence are not easily correctable, and patients are often able to achieve excellent levels of adherence despite the presence of one or more factors associated with poor adherence. Moreover, research has consistently shown that clinicians do not accurately predict their patients' levels of adherence. **Hence, the persistence of one or more potential barriers to adherence should not prompt denial of HAART to patients who otherwise qualify for treatment.**

Practical strategies to improve adherence prior to initiation of HAART include:

- ✓ ***educating the patient*** regarding the anticipated benefits of HAART, the potential for treatment failure and viral resistance associated with suboptimal adherence, and possible side effects of the medications;
- ✓ ***treating potential barriers to adherence*** prior to initiation of therapy, such as substance abuse or mental health disorders;
- ✓ ***recruiting support*** from other members of the healthcare team, members of the patient's social network of friends and family, and community-based organisations to reinforce the importance of adherence and assist with overcoming barriers to adherence;
- ✓ ***negotiating a treatment plan*** to which the patient is committed, taking into consideration the patient's daily routines, meal and work schedules, and co-morbid medical conditions;
- ✓ ***simplifying the regimen*** as much as possible by favouring regimens that include a low pill burden, once- or twice-daily dosing, and minimal food restrictions;
- ✓ ***providing a written or pictorial schedule*** for taking the medications;
- ✓ ***considering the use of automated reminders*** such as pagers, alarms, and pill boxes; and
- ✓ ***considering a trial period of simulated therapy***, using candy instead of actual pills, to identify potential obstacles to adherence.

A more detailed discussion of adherence, including a sample patient adherence questionnaire, can be found in [Chapter 1: Comprehensive Management of Persons with HIV Infection](#).

## ***TREATMENT OF CO-MORBID OPPORTUNISTIC INFECTIONS (OIs)***

Many patients will be diagnosed with HIV infection at the time they are diagnosed with an OI. Development of an OI reflects significant damage to the immune system, implying that HAART should be initiated as soon as possible. However, in such situations, it may be advantageous to initiate treatment of the OI first and then to initiate HAART shortly thereafter (e.g. a few weeks later). The risks associated with this slight delay in initiation of HAART are often outweighed by the advantages of 1) allowing time for the patient to psychologically adjust to the diagnosis of HIV infection and to prepare for HAART; 2) allowing time for adherence issues to be adequately addressed; and 3) reduction in the likelihood of significant immune reconstitution syndrome (IRS) involving the OI.

IRS represents an inflammatory response to an OI by an immune system that has been invigorated by the recent initiation of HAART. Clinically, IRS typically presents as fevers, sweats, lymphadenopathy, fatigue, and other features characteristic of the underlying OI. These signs and symptoms typically develop within the first several weeks after initiation of HAART. Often, the OI responsible for IRS represents a new diagnosis, having remained clinically ‘silent’ in the face of a severely depleted immune system. Care must be taken to distinguish IRS from a truly new OI in the patient who has recently initiated HAART. Management of IRS typically involves continuation of HAART, initiation or continuation of treatment for the responsible OI, and use of non-steroidal anti-inflammatory drugs (NSAIDs). Steroids, such as prednisone, are often used in the management of severe cases of IRS. Further discussion of IRS can be found in *Chapter V: Recommendations for the Treatment of Opportunistic Infections (OIs) among Adults and Adolescents* and in *Chapter X: Diagnosis and Treatment of Opportunistic Infections (OIs) among HIV-Exposed and –Infected Children*.

## ***LABORATORY MONITORING PRIOR TO INITIATION OF HAART***

Prior to initiation of HAART, it is useful to check haematologic and chemistry indices in order to screen for abnormalities and to establish baseline levels for future comparison. It is also helpful to check a baseline CD4+ T cell count and (where available) an HIV viral load, so that the immunologic (and virologic) response to HAART may be measured against pre-therapy baseline levels. **However, if clinically indicated, HAART should not be delayed where resources are scarce or laboratory testing is not readily available to document baseline laboratory values.** Pregnancy testing prior to initiation of HAART is recommended for women of childbearing potential. See *Appendix E* for details regarding baseline and follow-up laboratory monitoring.

## ***SELECTION OF THE INITIAL HAART REGIMEN***

The optimal HAART regimen provides potency and durability with a simple dosing schedule and minimal adverse effects while preserving future treatment options in the event of treatment failure. Fortunately, the introduction of additional ARV agents and the development of combination pills over the past several years have resulted in a number of potent therapeutic options that are simpler and better tolerated than earlier HAART regimens.

### ***PI-Based vs. NNRTI-Based vs. Triple-NRTI Regimens***

Initial HAART regimens typically consist of a combination of two NRTIs (the *nucleoside backbone*) plus an NNRTI or a PI (which may or may not be boosted by low doses of RTV\*). HAART regimens consisting of a dual nucleoside backbone plus an NNRTI can be described as *NNRTI-based* regimens, whereas *PI-based* regimens consist of a dual nucleoside backbone plus a PI (sometimes boosted by RTV\*). HAART regimens consisting of three NRTIs (*triple NRTI regimens*) such as AZT plus 3TC plus ABC can also be considered for initial therapy, but are not generally recommended unless significant contra-indications exist to more potent conventional PI- or NNRTI-based regimens. Triple NRTI

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\*See *Appendix B* for background and dosing information regarding the use of low-dose RTV to boost serum levels of other PIs.

combinations that include TDF plus ABC or TDF plus ddi appear to perform particularly poorly and should be avoided.

For most patients in the Caribbean region, the advantages of an NNRTI-based initial HAART regimen outweigh those of a PI-based regimen, chiefly due to the simplicity of these regimens (low pill burden, once- or twice-daily dosing schedule without significant food restrictions, no refrigeration requirements); a wide availability of NVP and EFV (including combination tablets for NVP); generally favourable tolerability; and potency.

**Table 3:** ARVs for Treatment of HIV Infection. (Agents in **bold** are commonly available in the Caribbean. Commonly used abbreviations are in parentheses. Note that many of these agents are available in combination forms of two or more medications combined into a single pill.)

NRTIs	NNRTIs	PIs	FUSION INHIBITORS
zidovudine (ZDV, AZT)	nevirapine (NVP)	nelfinavir (NFV)	enfuvirtide (ENF)
lamivudine (3TC)	efavirenz (EFV, EFZ)	ritonavir (RTV)	
stavudine (d4T)	delavirdine (DLV)	saquinavir (SQV)	
didanosine (ddI)		indinavir (IDV)	
abacavir (ABC)		lopinavir/ritonavir (LPV/r)	
tenofovir (TDF)		atazanavir (ATV)	
emtricitabine (FTC)		amprenavir (APV)	
zalcitabine (ddC)		fos-amprenavir (fos-APV)	

**Table 4:** Combination NRTI/NNRTI Tablets for Antiretroviral Therapy. (Listed are common co-formulations of ARV agents. Please note that this list may not be complete given that new formulations may have been developed since these guidelines were published, and not all formulations may be readily available in the region.)

COMBINATION TABLET NAME(S)	COMPONENT MEDICATIONS
Combivir <sup>®</sup>	AZT/3TC
Trizivir <sup>®</sup>	AZT/3TC/ABC
Tri-immune <sup>®</sup>	d4T/3TC/NVP
Duovir <sup>®</sup>	AZT/3TC
Duovir-N <sup>®</sup>	AZT/3TC/NVP

A more comprehensive review of these ARV agents, including adult dosing schedules, metabolism, and common adverse effects can be found in [Appendix A](#).

## ***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/mm<sup>3</sup> 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/mm<sup>3</sup> 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. In addition to this, PIs should ideally be preserved for 2<sup>nd</sup> line regimens. 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 5](#) for preferred initial regimens, along with their respective advantages and disadvantages; see [Table 6](#) for alternative initial HAART options. For HAART considerations in

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\*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).

patients with co-morbid conditions (e.g. hepatitis, diabetes, or tuberculosis [TB]), see section titled “HAART Considerations for Patients with Co-Morbid Diseases” in this chapter. For ART considerations in pregnant women, see *Chapter VII: Antiretroviral Therapy in Pregnant Women and Prevention of Mother-to-Child Transmission of HIV*.

**Table 5: Preferred Initial HAART Regimens**

REGIMEN	USE IN TB CO-INFECTION?	PILLS/DAY	ADVANTAGES	DISADVANTAGES
<b>AZT + 3TC* + EFV</b>	Yes; dose adjustments required in rifampicin-based regimens ( <i>see Table 9, page IV-18 for details</i> )	3-5	<ul style="list-style-type: none"> <li>• Simple</li> <li>• Highly potent</li> <li>• Generally well-tolerated</li> <li>• Less potential for toxicities associated with mitochondrial dysfunction**</li> <li>• Less potential for skin and liver toxicity than NVP-based regimens</li> </ul>	<ul style="list-style-type: none"> <li>• <b>Contra-indicated in women who are pregnant or may become pregnant (EFV)<sup>†</sup></b></li> <li>• Potential for EFV-associated CNS side effects<sup>‡</sup></li> <li>• Potential for AZT-associated anaemia</li> </ul>
<b>AZT + 3TC + NVP<sup>§</sup></b>	Yes in rifampicin-free continuation phase of TB treatment. Use with caution in rifampicin-based regimens	2 - 6	<ul style="list-style-type: none"> <li>• Simple</li> <li>• Highly potent</li> <li>• Generally well-tolerated</li> <li>• Less potential for toxicities associated with mitochondrial dysfunction**</li> <li>• Not contra-indicated in pregnancy</li> <li>• Less potential for EFV-associated CNS side effects</li> </ul>	<ul style="list-style-type: none"> <li>• Higher potential for liver, skin toxicity than EFV-based regimens<sup>††</sup></li> <li>• Potential for AZT-associated anaemia</li> </ul>
<b>d4T + 3TC + EFV</b>	Yes; dose adjustments required in rifampicin-based regimens ( <i>see Table 9, page IV-18 for details</i> )	5-7	<ul style="list-style-type: none"> <li>• Simple</li> <li>• Highly potent</li> <li>• Generally well-tolerated</li> <li>• Unlikely to induce or worsen anaemia</li> <li>• Less potential for skin and liver toxicity than NVP-based regimens</li> </ul>	<ul style="list-style-type: none"> <li>• <b>Contra-indicated in women who are pregnant or may become pregnant (EFV)</b></li> <li>• Potential for EFV-associated CNS side effects</li> <li>• Higher potential for toxicities associated with mitochondrial dysfunction**</li> </ul>
<b>d4T + 3TC + NVP<sup>§</sup></b>	Yes in rifampicin-free continuation phase of TB treatment. Use with caution in rifampicin-based regimens	2 - 6	<ul style="list-style-type: none"> <li>• Simple</li> <li>• Highly potent</li> <li>• Generally well-tolerated</li> <li>• Unlikely to induce or worsen anaemia</li> <li>• Not contra-indicated in pregnancy</li> <li>• Less potential for EFV-associated CNS side effects</li> </ul>	<ul style="list-style-type: none"> <li>• Higher potential for liver, skin toxicity than EFV-based regimens<sup>††</sup></li> <li>• Higher potential for toxicities associated with mitochondrial dysfunction**</li> </ul>

\* FTC may be substituted for 3TC, where available.

<sup>†</sup>Severe neurological birth defects have been documented in infants of women exposed to EFV during pregnancy.

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

<sup>§</sup>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.

<sup>††</sup>Risk of NVP-induced hepatotoxicity is especially elevated in women with pre-HAART CD4+ T cell counts of >250 cells/mm<sup>3</sup> and in men with pre-HAART CD4+ T cell counts of >400 cells/mm<sup>3</sup>.

**Table 6: Alternative Initial HAART Regimens**

REGIMEN - EXAMPLES	USE IN TB CO- INFECTION?	PILLS/DAY	ADVANTAGES	DISADVANTAGES
<b>3 NRTIs</b> <ul style="list-style-type: none"> <li>• AZT + 3TC + ABC</li> <li>• d4T + 3TC + ABC</li> </ul>	Yes; no dose adjustments necessary	2 - 6	<ul style="list-style-type: none"> <li>• Generally well-tolerated</li> <li>• Potentially fewer metabolic complications*</li> <li>• Preserves PI and NNRTI options</li> </ul>	<ul style="list-style-type: none"> <li>• Lower potency than EFV- or LPV/r-based regimens</li> <li>• Potential for ABC hypersensitivity</li> </ul>
<b>TDF + 3TC<sup>†</sup> + NNRTI<sup>‡</sup></b> <ul style="list-style-type: none"> <li>• TDF + 3TC + EFV</li> <li>• TDF + 3TC + NVP</li> </ul>	Yes. See <a href="#">Table 9, page IV-18</a> for details regarding dose adjustments when used with rifampicin-based regimens	3 - 6	<ul style="list-style-type: none"> <li>• Highly potent</li> <li>• Low pill burden</li> <li>• Once-daily option with EFV may improve adherence</li> </ul>	<ul style="list-style-type: none"> <li>• TDF not widely available in Caribbean</li> <li>• Potential for liver, skin toxicity (NVP&gt;EFV)</li> <li>• Teratogenicity (EFV)</li> <li>• Second-line options may be limited</li> </ul>
<b>2 NRTIs + LPV/r</b> <ul style="list-style-type: none"> <li>• AZT + 3TC + LPV/r</li> <li>• d4T + 3TC + LPV/r</li> </ul>	Yes. See <a href="#">Table 9, page IV-18</a> for details regarding dose adjustments when used with rifampicin-based regimens	7 - 10	<ul style="list-style-type: none"> <li>• Highly potent</li> <li>• Less potential for liver, skin toxicity than NNRTI-based regimens</li> </ul>	<ul style="list-style-type: none"> <li>• LPV/r not commonly available in the Caribbean</li> <li>• High pill burden</li> <li>• High potential for drug-drug interactions</li> <li>• GI side effects common (LPV/r)</li> <li>• Refrigeration requirement (LPV/r)</li> </ul>
<b>2 NRTIs + NFV</b> <ul style="list-style-type: none"> <li>• AZT + 3TC + NFV</li> <li>• d4T + 3TC + NFV</li> </ul>	Co-administration of NFV and rifampicin contra-indicated; see <a href="#">Table 9, page IV-18</a>	6 - 14	<ul style="list-style-type: none"> <li>• Reasonably well-tolerated</li> <li>• No refrigeration requirements</li> <li>• Fewer drug interactions than other PI-based regimens</li> </ul>	<ul style="list-style-type: none"> <li>• High pill burden<sup>§</sup></li> <li>• Lower potency than EFV- or LPV/r-based regimens</li> <li>• Diarrhoea common (NFV)</li> </ul>
<b>2 NRTIs + ATV (or r/ATV)</b> <ul style="list-style-type: none"> <li>• AZT + 3TC + ATV</li> <li>• d4T + 3TC + ATV</li> <li>• TDF + 3TC + ATV</li> </ul>	Co-administration of ATV (or r/ATV) and rifampicin contra-indicated; see <a href="#">Table 9, page IV-18</a>	4 - 7	<ul style="list-style-type: none"> <li>• Well-tolerated</li> <li>• Low pill burden</li> <li>• No refrigeration requirements</li> <li>• Higher potency than NFV-based regimens</li> <li>• Unlike other PIs, ATV not associated with dyslipidaemia</li> <li>• TDF/3TC/ATV can be dosed once-daily</li> </ul>	<ul style="list-style-type: none"> <li>• ATV not widely available in the Caribbean</li> <li>• Unclear if potency equivalent to EFV- or LPV/r-based regimens (though comparable potency likely if ATV is boosted by low-dose RTV)</li> </ul>

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

<sup>†</sup> FTC may be substituted for 3TC, where available.

<sup>‡</sup>**Do not use EFV in women who are pregnant or at risk for pregnancy.**

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

### ***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 *Table 9* and *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.

### ***PATIENT FOLLOW-UP AND MONITORING AFTER INITIATION OF THERAPY***

After HAART is initiated, close monitoring of the patient is warranted for toxicity and adherence. A follow-up visit with the prescribing clinician or an associated community healthcare professional is recommended within two weeks of initiation of ARV therapy. At this visit, adherence issues can be re-addressed and the patient can be assessed for any clinical evidence of drug toxicity.

### ***Adherence***

The importance of adherence for those initiating HAART cannot be overemphasised. Studies suggest that adherence is especially critical in the first few months of ARV therapy, when the HIV viral load is expected to decline rapidly. Suboptimal adherence can rapidly lead to the development of drug resistance, ultimately resulting in regimen failure as well as the loss of antiretroviral options for salvage regimens.

Assessment of adherence should therefore be performed at every visit in order to identify and correct any potential barriers. A trusting and non-judgmental relationship between the clinician and patient is critical in this regard. Studies have found that clinicians do not reliably predict their patients' levels of adherence; more accurate methods of assessing adherence include patient recollection of missed doses and pharmacy refill records. A sample patient adherence questionnaire, as well as a more thorough discussion of adherence, can be found in *Chapter I: Comprehensive Management of Persons with HIV Infection*.

Key strategies that may be useful in promoting adherence in patients who have recently initiated therapy include:

- ✓ **establishing trust**
- ✓ **closely monitoring adherence** at routine visits
- ✓ **providing access between visits** for questions or problems
- ✓ **involving patient's social network** to provide ongoing adherence support
- ✓ **adding adherence assessment and reinforcement to job descriptions of support team members**, such as nurses, pharmacists, case managers, and clinicians' assistants

### ***Laboratory Monitoring***

Periodic laboratory monitoring is also recommended to screen for toxic effects of antiretroviral medications and to assess the patient's immunologic and (where available) virologic response to therapy. However, clinical assessment without laboratory monitoring is reasonable if laboratory testing is not readily available.

*Appendix E* summarises recommended laboratory testing for patients on HAART. The laboratory monitoring that is recommended depends on the HAART regimen that is prescribed and on the patient's co-morbid conditions and past medical history. For example, increased vigilance for liver toxicity is warranted in individuals with a history of chronic hepatitis who initiate antiretroviral therapy. Because most drug-related toxicities appear within the first few months of introduction of the drug, it is reasonable to decrease the frequency of monitoring in patients who initially display no evidence of toxicity. Similarly, the frequency of CD4+ T cell count monitoring may be decreased in individuals who maintain

excellent adherence to their medications and who demonstrate sustained clinical improvement. While HIV viral load testing is useful in assessing efficacy of treatment and early detection of treatment failure, it is not mandatory for the management of these patients. Obviously, clinical signs or symptoms that suggest toxicity warrant prompt investigation. Hence, this table represents a rough guideline only and should be tailored to the individual patient.

### 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 antiretroviral agents resolve within one to three months of initiation of therapy. If the adverse effect is severe enough to require modification of the regimen, substitution of the offending drug with another antiretroviral agent is an option if it can be reasonably deduced which agent is responsible for the side effect in question. *Table 7* 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 7:** Common Adverse Drug Reactions Associated with First-Line HAART Regimens and Recommended Drug Substitutions.\* For severe reactions, consider discontinuation of entire HAART regimen until clinical resolution.

REGIMEN	TOXICITY	DRUG SUBSTITUTION
d4T/3TC/NVP	• d4T-related neuropathy or pancreatitis	• Switch d4T → AZT
	• d4T-related lipodystrophy	• Switch d4T → TDF or ABC <sup>†</sup>
	• NVP-related severe hepatotoxicity	• Switch NVP → EFV <sup>‡</sup>
	• NVP-related severe rash (but not life-threatening)	• Switch NVP → EFV <sup>‡</sup>
	• NVP-related life-threatening rash (e.g. Stevens-Johnson syndrome)	• Switch NVP → PI <sup>§</sup>
AZT/3TC/NVP	• AZT-related persistent GI intolerance or severe haematological toxicity	• Switch AZT → d4T
	• NVP-related severe hepatotoxicity	• Switch NVP → EFV <sup>‡</sup>
	• NVP-related severe rash (but not life-threatening)	• Switch NVP → EFV <sup>‡</sup>

\* Adapted from the World Health Organisation. Table C: Major potential toxicities of first-line ARV regimens recommended drug substitutions in Revised WHO guidelines for scaling up antiretroviral therapy in resource-limited settings. 2003 revision. Available at: [http://www.who.int/hiv/pub/prev\\_care/en/arvrevision2003en.pdf](http://www.who.int/hiv/pub/prev_care/en/arvrevision2003en.pdf).

<sup>†</sup>Switching out d4T appears to reduce, and may even reverse, lipodystrophy (though very slowly). TDF and ABC represent the best alternatives to d4T in this setting, but their availability in the Caribbean is limited; AZT is a reasonable alternative where TDF and ABC are not available.

<sup>‡</sup>**Except in pregnancy.** If the patient is pregnant or at risk for becoming pregnant, substitute a PI (preferred) or ABC.

<sup>§</sup>Recommended PIs include LPV/r or SQV/r; NFV and IDV/r are acceptable alternatives. Consider use of triple NRTI regimen or EFV if PI not available; theoretical potential for cross-reaction with EFV.

	<ul style="list-style-type: none"> <li>• NVP-related life-threatening rash (e.g. Stevens-Johnson syndrome)</li> </ul>	<ul style="list-style-type: none"> <li>• Switch NVP → PI<sup>§</sup></li> </ul>
REGIMEN	TOXICITY	DRUG SUBSTITUTION
d4T/3TC/EFV	<ul style="list-style-type: none"> <li>• d4T-related neuropathy or pancreatitis</li> </ul>	<ul style="list-style-type: none"> <li>• Switch d4T → AZT</li> </ul>
	<ul style="list-style-type: none"> <li>• d4T-related lipotrophy</li> </ul>	<ul style="list-style-type: none"> <li>• Switch d4T → TDF or ABC<sup>†</sup></li> </ul>
	<ul style="list-style-type: none"> <li>• EFV-related persistent CNS toxicity</li> </ul>	<ul style="list-style-type: none"> <li>• Switch EFV → NVP</li> </ul>
	<ul style="list-style-type: none"> <li>• EFV-related skin toxicity (severe)</li> </ul>	<ul style="list-style-type: none"> <li>• Switch EFV → PI or triple NRTI-based regimen</li> </ul>
AZT/3TC/EFV	<ul style="list-style-type: none"> <li>• AZT-related persistent GI intolerance or severe haematological toxicity</li> </ul>	<ul style="list-style-type: none"> <li>• Switch AZT → d4T</li> </ul>
	<ul style="list-style-type: none"> <li>• EFV-related persistent CNS toxicity</li> </ul>	<ul style="list-style-type: none"> <li>• Switch EFV → NVP</li> </ul>
	<ul style="list-style-type: none"> <li>• EFV-related skin toxicity (severe)</li> </ul>	<ul style="list-style-type: none"> <li>• Switch EFV → PI or 3 NRTI-based regimen</li> </ul>

Occasionally, severe HAART-related toxicity requires discontinuation of all ARV agents. In such circumstances, it is best to discontinue all of the medications simultaneously, because continuation of therapy with only one or two ARV agents is associated with the development of drug resistance. 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. 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.

### TREATMENT FAILURE

Treatment failure refers to the absence of a sustained favourable response to antiretroviral therapy. 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 in order to prevent HIV disease progression and the development of further resistance to antiretroviral agents. Laboratory testing can be useful both to establish treatment failure and to guide 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 chapter.

### TREATMENT FAILURE: CLINICAL DEFINITION

Treatment failure should be suspected if progression of HIV disease continues following initiation of HAART **or** if no clinical improvement occurs three months after initiation of therapy. Clinical indicators of HIV disease progression include weight loss, papular prurigo, oral candidiasis, fevers and night sweats, or chronic diarrhoea. Clinicians must be careful to distinguish suspected HIV disease progression from IRS, which can also manifest with fevers, night sweats, and fatigue; however, IRS typically resolves within a couple of months following initiation of HAART. Further discussion of IRS can be found in the

introduction to *Chapter V: Recommendations for the Treatment of Opportunistic Infections (OIs) among Adults and Adolescents.*

Laboratory testing is highly recommended in the setting of suspected clinical treatment failure. Ideally, a CD4+ T cell count and HIV viral load should be checked, and the results reviewed with an expert HIV clinician, followed by immediate revision of the HAART regimen if indicated. If resources do not permit CD4+ T cell count and viral load testing, these guidelines recommend addressing adherence and tolerance issues, continuing the current regimen if tolerated, and re-assessing the patient in another three months. DOT may also be considered where feasible. Laboratory testing, especially viral load testing, is strongly recommended if treatment failure is still suspected six months following initiation of HAART. Laboratory results should again 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 recommended, as discussed below.

**TREATMENT FAILURE: IMMUNOLOGICAL DEFINITION**

Treatment failure should be suspected if the CD4+ T cell count declines or fails to rise within four to six months following initiation of HAART. The World Health Organisation (WHO) defines immunologic treatment failure as:

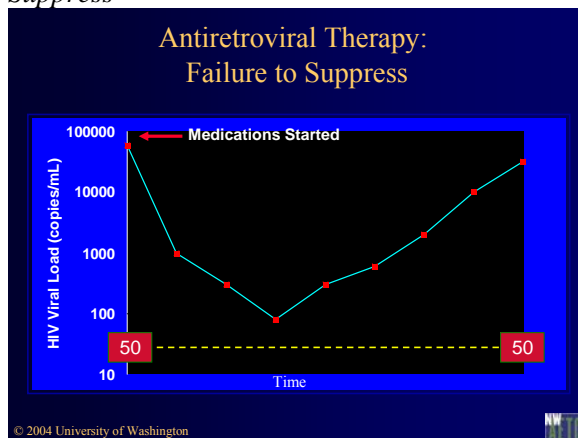
- a fall of over 30% in the CD4+ T cell count from the peak value; **or**
- a return of the CD4+ T cell count to or below the baseline (pre-HAART) CD4+ T cell count.

HAART-associated virologic suppression is typically associated with a significant rise in both the absolute and percentage of CD4+ T cells within three to six months of starting HAART, as depicted in *Figure 1*. However, discordant responses are sometimes observed in which full virologic suppression is achieved on HAART but the CD4+ T cell count fails to rise significantly or even continues to decline. The reasons for these discordant responses remain unclear, and management options should be reviewed with an expert HIV clinician. It is therefore strongly recommended that HIV viral load testing be performed in the setting of immunological treatment failure.

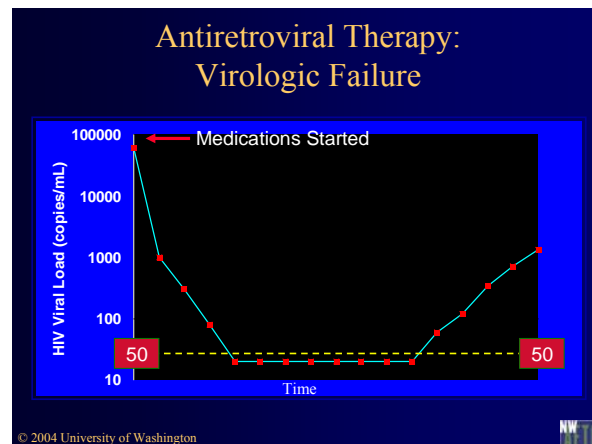
**TREATMENT FAILURE: VIROLOGIC DEFINITION**

With successful initial HAART, the HIV viral load is expected to decline by at least tenfold (one log<sub>10</sub>) 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, as depicted in *Figure 1*. Treatment failure can be defined by the absence of such a decline in HIV viral loads 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*), as depicted in *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 in order to discourage the development of drug resistance and to preserve effective treatment options.

**Figure 3: Antiretroviral Therapy: Failure to Suppress**



**Figure 4: Antiretroviral Therapy: Virologic Failure**



## **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 HAART 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. However, it is also clear that many patients are able to maintain clinical and immunologic stability on salvage HAART regimens, even if those regimens fail to achieve an undetectable viral load.

### ***HIV RESISTANCE TO ANTIRETROVIRAL THERAPY***

Treatment failure often (though not always) occurs because a patient's strain of HIV has developed resistance to one or more of his/her antiretroviral medications. The manner by which HIV develops resistance to ARVs 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 antiretroviral medications 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 sub-therapeutic drug levels in the blood, which could lead to the development of resistance.

Cross-resistance between ARVs 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*. Cross-resistance is not as common within the NRTI and PI classes, but can occur. 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. For example, patients failing an NNRTI-based initial treatment regimen commonly develop one or more mutations that confer high-level resistance to all available NNRTI medications. Hence, a second-line regimen for these patients should be PI-based rather than NNRTI-based. These concepts are discussed more fully below and are summarised in [Table 8](#). A more detailed discussion of antiretroviral resistance and resistance assays can be found in [Appendix F](#).

### ***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 7](#). For example, if a patient 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.

If the initial HAART regimen was discontinued due to treatment failure, however, it is likely that drug resistance to one or more ARVs in the initial regimen has developed. The next HAART regimen must be constructed carefully to account for this potential resistance. Where available, antiretroviral resistance testing is strongly recommended to help guide the design of the second-line regimen. If resistance-testing 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. Therefore, second-line regimens for patients who initiated an NNRTI-based regimen generally involve replacement of the NNRTI with a PI. RTV-boosting of the PI is generally recommended because this is associated with higher potency, reducing the risk of failure of the second-line regimen. Conversely, initial PI-based regimens should generally be replaced with NNRTI-based regimens.

Paradoxically, many HIV experts recommend including 3TC in second-line regimens of patients who have failed initial 3TC-containing regimens. This is because the mutation that confers resistance to 3TC also diminishes the replicative capacity of the virus. Including 3TC in the second-line regimen pressures HIV to maintain this mutation, thereby indirectly helping to suppress viral replication. Furthermore, 3TC is generally well-tolerated and has a low pill burden, so adding it to three other ARV agents is usually well-tolerated. It should be noted, however, that clinical evidence substantiating this theoretical benefit is lacking.

Most initial HAART regimens will also contain either AZT or d4T. Unfortunately, AZT and d4T share very 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 combined with either TDF or ABC. Unfortunately, TDF and ABC are not commonly available in the Caribbean. However, 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 TDF and ABC are not available, AZT or d4T may be retained in second-line regimens even if the initial regimen contained one of these agents.

*Table 8* presents suggested second-line regimens for patients who have experienced treatment failure on their initial HAART regimen in situations where resistance testing is not available to help guide decision-making.

**Table 8: Second-Line Regimen Recommendations for Treatment Failure**

FAILED FIRST-LINE REGIMEN	SECOND-LINE REGIMEN OPTIONS*	COMMENTS
d4T + 3TC + EFV <b>or</b> d4T + 3TC + NVP	ABC + ddI + PI/r <sup>†</sup> <b>or</b> AZT + ddI + PI/r <b>or</b> TDF + ddI <sup>‡</sup> + PI/r <b>or</b> TDF + (AZT or d4T or ABC) + PI/r <b>or</b> ABC + ddI + AZT + PI/r	<ul style="list-style-type: none"> <li>• ABC not widely available; beware of ABC hypersensitivity</li> <li>• TDF not widely available</li> <li>• Resistance to d4T will develop late in failure of this regimen, potentially allowing the use of d4T or AZT in a subsequent 2<sup>nd</sup> line regimen</li> </ul>
AZT + 3TC + EFV <b>or</b> AZT + 3TC + NVP	ABC + ddI + PI/r <b>or</b> AZT + ddI + PI/r <b>or</b> TDF + ddI + PI/r <b>or</b> TDF + (AZT or d4T or ABC) + PI/r <b>or</b> ABC + ddI + AZT + PI/r	<ul style="list-style-type: none"> <li>• TDF not widely available</li> <li>• ABC not widely available; beware of ABC hypersensitivity</li> <li>• Resistance to AZT will develop late in failure of this regimen, potentially allowing the use of d4T or AZT in a subsequent 2<sup>nd</sup> line regimen</li> </ul>
2 NRTIs + (PI or PI/r)	2 different NRTIs + (EFV or NVP) <b>or</b> 2 different NRTIs + PI/r	<ul style="list-style-type: none"> <li>• See patterns above for NRTI selection, bearing in mind that use of TDF + ddI + NNRTI no longer recommended for HAART</li> <li>• Because PI resistance develops relatively slowly, a PI/r–based second-line therapy may be effective even for patients who failed initial PI-based therapy</li> </ul>
AZT + 3TC + ABC	TDF + ddI + PI/r <b>or</b> TDF + ddI + NFV <b>or</b> TDF + (AZT or d4T) + PI/r <b>or</b> Substitute ABC for TDF in above options <b>or</b> Substitute d4T for TDF in above options	<ul style="list-style-type: none"> <li>• When TDF and ddI are taken together, ddI dose is lowered and no food restrictions</li> <li>• Use of TDF + ddI + NNRTI no longer recommended for HAART</li> <li>• RTV-boosting of PI recommended for higher potency</li> <li>• Potency of ABC in this setting questionable but may retain some activity despite failure of first-line regimen</li> <li>• d4T + ddI combination not generally recommended due to excess toxicity</li> </ul>

\*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 induced by the signature 3TC resistance mutation (see text for further explanation).

<sup>†</sup>PI/r = RTV-boosted PI (e.g. LPV/r; IDV/r; SQV/r)

<sup>‡</sup> Dosage of ddI should be lowered to 250mg when combined with TDF.

## 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 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 HAART 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.

## HAART CONSIDERATIONS FOR PATIENTS WITH CO-MORBID DISEASES

### PATIENTS WITH HIV AND TUBERCULOSIS (TB)

Patients co-infected with HIV and TB present complex treatment issues, and consultation with an expert in the management of these diseases is highly recommended. Significant drug interactions requiring dose adjustments exist between many of the antiretroviral and the rifamycins, as summarised below in Table 10.

**Table 9:** (source: <http://www.madisonclinic.org>, Brad Kosel, PharmD, (c) University of Washington, 2005).

Drug Interactions with Tuberculosis Agents					
	rifabutin (RFB)		rifampin (RFP)		
Antiretroviral	ARV Dose	RFB dose	ARV Dose	RFP dose	Details
efavirenz (EFV)	600mg QD	450mg QD or 600mg 3 times a week	800mg QD or 600mg QD	600mg QD	EFV <b>decreases</b> RFB by 32% RFB has no effect on EFV RFP <b>decreases</b> EFV by 26% More data needed for RFP/EFV
nevirapine (NVP)	200mg BID	300mg QD	200mg BID	600mg QD	Minor interaction with RFP/NVP RFP <b>reduces</b> NVP by 31-58% Caution is warranted
delavirdine (DLV)	Contraindicated	Contraindicated	Contraindicated	Contraindicated	RFB <b>decreases</b> DLV by 82% RFB <b>decreases</b> DLV by 97% DLV <b>increases</b> RFB by 230%
atazanavir (ATV)	400mg QD	150mg QOD (i.e. 75% reduction of standard dose)	Contraindicated	Contraindicated	ATV <b>increases</b> RFB level RFP <b>reduces</b> ATV with and without RTV
fosamprenavir (FAPV)	1400mg BID	150mg QD or 300mg 3 times a week	Contraindicated	Contraindicated	APV <b>increases</b> RFB by 204% RFB <b>reduces</b> APV by 15% RFP <b>reduces</b> APV by 82%
indinavir (IDV)	1000-1200mg Q8H	150mg QD	Contraindicated	Contraindicated	IDV <b>increases</b> RFB by 60% IDV <b>increases</b> RFP by 73% RFB <b>reduces</b> IDV by 32% RFP <b>reduces</b> IDV by 89%
lopinavir/RTV (LPV/r)	400mg/100mg BID	150mg QOD or 3 times a week	400mg/400mg BID 800mg/200mg BID	600mg QD	LPV/r <b>increases</b> RFB RFB has no effect on LPV/r RFP <b>reduces</b> LPV/r by 75%

Drug Interactions with Tuberculosis Agents					
	rifabutin (RFB)		rifampin (RFP)		
nelfinavir (NFV)	1250mg BID	150mg QD	Contraindicated	Contraindicated	NFV increases RFB by 200% RFB <b>reduces</b> NFV by 32% RFP <b>reduces</b> NFV by 82%
saquinavir/RTV (SQV)	400mg/400mg BID	150mg QOD or 3 times a week	400/400mg BID	600mg QD	RFB <b>reduces</b> SQV by 40% RFP <b>reduces</b> SQV by 84% Limited data for use with RFP
IDV/RTV	800mg/100mg 800mg/200mg (both BID)	150mg QOD or 3 times a week	Contraindicated	Contraindicated	No data on IDV/RTV with RFB RTV is likely to overcome Induction by RFB Questionable levels with RFP
ATV/RTV	300mg/100mg QD	150mg QOD or 3 times a week	Contraindicated	Contraindicated	RFB does not affect ATV RFP <b>reduces</b> ATV in the presence of RTV
FAPV/RTV	700mg/100mg BID 1400mg/200mg QD	150mg QOD or 3 times a week	No Data	No Data	No data currently on the use of RFP with FAPV/RTV. Use is most likely contraindicated

Patients co-infected with HIV and TB may also exhibit a paradoxical worsening of TB-related signs and symptoms (e.g. night sweats, fevers, lymphadenopathy, and pulmonary findings) in the first several weeks after initiating HAART. These paradoxical reactions reflect IRS, and can be severe enough to require steroid therapy. The potential for severe IRS reactions to TB has prompted many expert clinicians to recommend that TB therapy be generally initiated before HAART. Further discussion of IRS and of the management of patients co-infected with HIV and TB can be found in [Chapter V: Recommendations for the Treatment of Opportunistic Infections \(OIs\) among Adults and Adolescents](#).

#### **PATIENTS WITH HIV AND DIABETES MELLITUS**

Many PIs, as well as the NNRTI EFV, have been associated with insulin resistance. Hence, diabetic patients should be monitored closely for possible worsening of glucose control after starting PI-containing HAART regimens, and the diabetic regimen may need to be intensified. Significant drug-drug interactions between ARVs and diabetic agents have not been described. The use of metformin with NRTI-containing ARV regimens may increase the risk of lactic acidosis, but this has not been clearly documented in clinical practice.

#### **PATIENTS WITH HIV AND CHRONIC LIVER DISEASE**

All classes of ARV agents have been associated with liver toxicity, so extra caution is warranted in prescribing HAART for patients with chronic liver disease. NVP and RTV have been associated with the highest risk of liver toxicity and should therefore be avoided if other options exist, though the risk of liver toxicity using low doses of RTV to boost another PI is not clear.

For patients with chronic hepatitis B (HBV) infection, inclusion of 3TC and/or TDF in the HAART regimen should be considered because these agents are potent inhibitors of HBV replication and are useful in the clinical management of this disease. However, patients who have a history of 3TC monotherapy while co-infected with HBV and HIV likely developed HIV resistance to 3TC, compromising the efficacy of this agent in HAART regimens. Discontinuation of either of these agents in a patient with chronic HBV can be associated with an acute exacerbation of HBV. Further discussion of

the management of patients co-infected with HIV and HBV can be found in [Chapter V: Recommendations for the Treatment of Opportunistic Infections \(OIs\) among Adults and Adolescents](#).

#### ***PATIENTS WITH HIV AND RENAL DISEASE***

Dose adjustment of some ARVs, especially the NRTIs, must be performed for patients with renal insufficiency or renal failure. Renal dosing for ARVs can generally be found in their respective packaging information.

#### ***PATIENTS WITH HIV AND OTHER SEXUALLY TRANSMITTED INFECTIONS (STIs)***

Co-morbid STIs are commonly encountered in persons infected with HIV. Prompt diagnosis and treatment of STIs reduces the risk of HIV transmission to others. Recent data suggest that treatment of chronic herpes simplex virus (HSV) infection reduces the risk of transmission of HSV, may reduce the risk of HIV transmission, and likely reduces the level of HIV viraemia in patients not on HAART. Further discussion of the management of patients co-infected with HIV and HSV can be found in [Chapter V: Recommendations for the Treatment of Opportunistic Infections \(OIs\) among Adults and Adolescents](#).

#### ***PATIENTS WITH HIV AND NEUROPSYCHIATRIC DISORDERS***

Significant drug-drug interactions exist between many ARVs and medications used to treat seizure disorders, bipolar affective disorder, and anxiety disorders, as described in [Appendix C](#). Use of certain agents in combination should be avoided altogether, while some agents can be combined safely as long as the dosage is adjusted appropriately. EFV should be used with caution in patients with a history of affective disorders.

### **METABOLIC COMPLICATIONS OF HAART AND HIV INFECTION**

A number of metabolic disturbances have been described in HIV-infected patients on HAART. Patients who have initiated treatment for HIV infection should be monitored carefully for development of these complications and managed appropriately, as outlined below. The exact aetiology of these complications is not clearly understood, and may reflect a multifactorial process involving antiretroviral medications, HIV itself, and host factors.

#### ***LACTIC ACIDOSIS AND HEPATIC STEATOSIS***

Lactic acidosis represents a rare but potentially fatal complication of antiretroviral therapy that has been linked to NRTIs and to HIV infection. NRTIs can inhibit human mitochondrial DNA polymerase gamma, an enzyme crucial for normal mitochondrial DNA replication. This inhibition results in depletion of mitochondrial DNA that compromises cellular oxidative phosphorylation. Evidence of mitochondrial DNA depletion can also be found in HIV-infected persons who have never received antiretroviral therapy, suggesting that HIV infection itself may contribute to mitochondrial dysfunction.

Clinically, this syndrome can range from asymptomatic hyperlactataemia to fatal lactic acidosis, often associated with hepatic steatosis. Development of this disorder appears to depend on the duration of NRTI exposure and on the specific ARVs used. d4T appears to be most commonly associated with lactic acidosis, followed by ddI and AZT, followed by 3TC and ABC. TDF appears to carry a low risk of mitochondrial toxicity as well. Pregnant women appear to be at greater risk for developing lactic acidosis, and deaths have been reported in women taking the combination of d4T plus ddI.

Physicians should maintain a high clinical suspicion for this syndrome, as symptoms are usually non-specific. Symptoms may include nausea, vomiting, abdominal pain and distension, diarrhoea, fatigue, myalgias, weight loss, and dyspnoea. An elevated lactic acid level establishes the diagnosis but requires sampling without a tourniquet, rapid transportation to a laboratory on ice, and processing within a few

hours. Other helpful laboratory indicators include elevated CPK, LDH, amylase, and aminotransferases, and low serum bicarbonate.

Lactic acidosis is treated with supportive care and discontinuation of ARVs until the syndrome resolves. Case reports have suggested that supplementation with high doses of vitamins involved in oxidative phosphorylation, such as riboflavin or L-carnitine, may hasten the recovery process. Consultation with an HIV expert is strongly recommended. Following resolution of the syndrome, HAART should be re-initiated cautiously and in consultation with an HIV expert, avoiding NRTIs such as d4T and ddI that are strongly associated with mitochondrial toxicity.

### ***LIPODYSTROPHY***

Lipodystrophy refers to changes in body habitus associated with HIV infection and antiretroviral therapy. Two distinct syndromes have been characterised: subcutaneous fat wasting (*lipoatrophy*) and central fat deposition (*lipohypertrophy*). Lipoatrophy is typically most apparent in the face and extremities, and has been associated with advanced HIV and with NRTIs, especially d4T. Central fat deposition in the viscera, breasts, and dorsocervical fat pad (*buffalo hump*) have also been described, though the pathophysiology of lipohypertrophy remains unclear. These changes in the distribution of fat are often, though not always, associated with dyslipidaemia and insulin resistance; some definitions of lipodystrophy include dyslipidaemia and insulin resistance, whereas others do not. A universally accepted case definition of lipodystrophy has not yet been established.

The optimal management of lipodystrophy is not known at this time. Lipoatrophy appears to improve, though very slowly, in patients who remove d4T from their ARV regimens and substitute NRTIs that have less potential for mitochondrial toxicity. Similar medication switch strategies have failed to consistently demonstrate a clinical benefit for patients with lipohypertrophy, though improvements have been documented following dietary and exercise modifications. Cosmetic plastic surgery options exist but are expensive and not widely available, and data regarding long-term outcomes are lacking.

### ***HYPERLIPIDAEMIA***

In the absence of ART, HIV infection can lead to dyslipidaemia, including lower HDL levels. HAART has been associated with elevated total cholesterol, LDL, and triglycerides. PIs (with the exception of ATV) have been most strongly associated with lipid abnormalities, though dyslipidaemia has also been documented in patients on NNRTI-based regimens as well as in regimens that include d4T. Recent data suggest that these abnormalities can lead to accelerated atherosclerosis and cardiovascular complications among HIV-infected persons. In general, patients with HIV/HAART-associated dyslipidaemia should be managed in a similar fashion as patients who are not infected with HIV. Low-fat diets, regular exercise, and smoking cessation represent first-line interventions. Fibrates and HMG-CoA reductase inhibitors (statins) can be helpful, but certain statins (e.g. simvastatin and lovastatin) should be avoided due to dangerous drug interactions with PIs. Pravastatin is the preferred agent; atovastatin may also be used at reduced doses.

### ***INSULIN RESISTANCE***

Hyperglycaemia, new onset diabetes, exacerbation of pre-existing diabetes, and diabetic ketoacidosis (DKA) have all been reported in HIV patients receiving HAART, especially in those receiving PIs. Symptoms of hyperglycaemia have been reported as early as sixty days following initiation of PIs. EFV has also been associated with insulin resistance. Routine fasting blood glucose measurements every three to four months should be performed for patients with no previous history of diabetes that are receiving PIs or EFV. Closer monitoring of glucose levels should be performed for pregnant women receiving PIs. Patients should be counselled to recognise symptoms of hyperglycaemia, such as polyuria, polydipsia, and polyphagia. Insulin resistance is usually treated by either switching to a non-PI/non-EFV-based regimen (if possible) or by supplementing the HAART regimen with oral hypoglycaemic agents or insulin.

## DISORDERS OF BONE METABOLISM

Avascular necrosis and decreased bone density have been documented in HIV-infected adults and children. It is unclear to what degree, if any, ARVs contribute to these disorders; some studies have linked use of PIs to osteopaenia and osteoporosis, while other data suggest a protective effect of PIs on bone mineralisation.

Recommended prevention and treatment measures for osteopaenia includes modification of other risk factors (e.g. smoking cessation, weight-bearing exercise) and adequate intake of calcium and vitamin D. Hormone replacement therapy may be considered in postmenopausal women. Bisphosphonates, such as alendronate, have demonstrated clinical efficacy for HIV-infected patients with osteoporosis.

Avascular necrosis most commonly involves the femoral or humeral head, leading to hip or shoulder pain. Risk factors for osteonecrosis include corticosteroid therapy, alcohol abuse, hyperlipidaemia, and hypercoagulable states. The diagnosis is typically made by x-ray or CT scan. There is no accepted medical therapy, and surgery may be needed to treat severe disabling symptoms.

**Table 10:** Selected Metabolic Complications in HIV

CONDITION	CAUSE	SYMPTOMS	DIAGNOSIS	TREATMENT
Hyperlactataemia/Lactic Acidosis/Hepatic Steatosis	Depletion of mitochondrial DNA  Drugs (e.g. d4T, ddI, AZT, 3TC, and ABC)	Nausea Vomiting Abdominal pain Diarrhoea Fatigue Dyspnoea Weight loss Myalgias	↑ venous lactate level ↑ CPK ↑ LDH ↑ amylase ↑ amino-transferases Low serum bicarbonate	Withdraw NRTIs (esp. ddI, d4T)  Supportive therapy  Consider vitamin supplementation (e.g. folate, L-carnitine)
Insulin Resistance  • Hyperglycaemia  • New onset diabetes  • Exacerbation of pre-existing diabetes and DKA	HAART, mainly PIs and EFV	Polyuria Polydipsia Polyphagia	Fasting blood glucose level  Monitor glucose every 3-4 months	Continue HAART  Diet/exercise  Add oral hypoglycaemic agents or insulin if necessary
Dyslipidaemia ↑ Total cholesterol ↑ LDL ↑ Triglycerides Decreased HDL	HAART; linked to PIs, EFV, and d4T	Associated with accelerated atherosclerosis and cardiovascular complications	Monitor lipid levels	Low-fat diets  Regular exercise  Smoking cessation  HMG-CoA inhibitors (statins) and/or fibrates

APPENDIX A: CHARACTERISTICS OF ANTIRETROVIRAL AGENTS\*

Table 11: Nucleoside Reverse Transcriptase Inhibitors (NRTIs)

GENERIC NAME (ABBREVIATION)/TRADE NAME	FORMULATION	DOSING RECOMMENDATIONS	FOOD EFFECT	ORAL BIO- AVAIL- ABILITY	SERUM HALF- LIFE	INTRA- CELLULAR HALF-LIFE	ELIMINATION	ADVERSE EVENTS
<b>Abacavir (ABC)</b> Ziagen <sup>®</sup> ; Trizivir <sup>®</sup> (w/ZDV + 3TC); Epzicom <sup>®</sup> (w/3TC)	<u>Ziagen<sup>®</sup></u> : 300mg tablets or 20mg/mL oral solution  <u>Trizivir<sup>®</sup></u> : ABC, 300mg + ZDV, 300mg + 3TC, 150mg  <u>Epzicom<sup>®</sup></u> : ABC, 600mg + 3TC, 300mg	300mg b.i.d; or 600mg q.d;  <b>OR</b> as Trizivir <sup>®</sup> , 1 tablet b.i.d  <b>OR</b> as Epzicom <sup>®</sup> , 1 tablet q.d	Take without regard to meals; alcohol increases ABC levels 41%; ABC has no effect on alcohol	83%	1.5 hours	12-26 hours	Metabolised by alcohol dehydrogenase and glucuronyl transferase  Renal excretion of metabolites 82%  Trizivir <sup>®</sup> and Epzicom <sup>®</sup> not for patients with CrCl <50mL/min	Hypersensitivity reaction that can be fatal; symptoms may include fever, rash, nausea, vomiting, malaise or fatigue, loss of appetite, respiratory symptoms such as sore throat, cough, shortness of breath
<b>Didanosine (ddI)</b> Videx <sup>®</sup> , Videx EC <sup>®</sup> , generic ddI enteric-coated (dose same as Videx EC <sup>®</sup> )	<u>Videx EC<sup>®</sup></u> : 125, 200 250, or 400mg capsules  <u>Videx<sup>®</sup> Buffered Tablets</u> : 25, 50, 100, 150, 200mg  <u>Videx<sup>®</sup> Buffered Powders</u> : 100, 167, 250mg	<u>Body Weight &gt;60kg</u> : 400mg q.d (buffered tablets or EC capsule); <b>OR</b> 200mg b.i.d (buffered tablets);  <u>With TDF</u> : 250mg/day  <u>&lt;60 kg</u> : 250mg q.d (buffered tablets or EC capsule); or 125mg b.i.d (buffered tablets)  <u>With TDF</u> : Appropriate dose not established; probably <250mg/day	Levels decrease 55%; take 1/2 hour before or 2 hours after meal	30-40%	1.5 hours	>20 hours	Renal excretion 50%  Dosage adjustment in renal insufficiency	Pancreatitis  Peripheral neuropathy  Nausea  Diarrhoea  Lactic acidosis with hepatic steatosis is a rare but potentially life-threatening toxicity associated with use of NRTIs

\* Adapted from: United States Department of Health & Human Services (DHHS). Guidelines for the Use of Antiretroviral Agents in HIV-Infected Adults & Adolescents. 29 Oct 2004. Last accessed 2 Mar 2005. Available at <http://www.aidsinfo.nih.gov>.

GENERIC NAME (ABBREVIATION)/TRADE NAME	FORMULATION	DOSING RECOMMENDATIONS	FOOD EFFECT	ORAL BIO- AVAIL- ABILITY	SERUM HALF- LIFE	INTRA- CELLULAR HALF-LIFE	ELIMINATION	ADVERSE EVENTS
<b>Emtricitabine (FTC)</b> Emtriva™; Truvada™ (w/TDF)	<u>Emtriva™</u> : 200mg hard gelatin capsule <u>Truvada™</u> : FTC, 200mg + TDF, 300mg	<u>Emtriva™</u> : 200mg q.d <u>Truvada™</u> : 1 tablet q.d	Take without regard to meals	93%	10 hours	>20 hours	Renal excretion Dosage adjustment in renal insufficiency Truvada™ not for patients with CrCl <30mL/min	Minimal toxicity Lactic acidosis with hepatic steatosis (rare but potentially life-threatening toxicity with use of NRTIs)
<b>Lamivudine (3TC)</b> Epivir®; Combivir® (w/ZDV); Epizicom® (w/ABC); Trizivir® (w/ZDV + ABC)	<u>Epivir®</u> : 150mg and 300mg tablets or 10mg/mL oral solution <u>Combivir®</u> : 3TC, 150mg + ZDV, 300mg <u>Epizicom®</u> : 3TC, 300mg + ABC, 600mg <u>Trizivir®</u> : <SUP®<sup> 3TC, 150mg ZDV, 300mg + ABC, 300mg	<u>Epivir®</u> : 150mg b.i.d <b>OR</b> 300mg q.d <u>Combivir®</u> : 1 tablet b.i.d <u>Epizicom®</u> : 1 tablet q.d <u>Trizivir®</u> : 1 tablet b.i.d	Take without regard to meals	86%	5-7 hours	18-22 hours	Renal excretion Dosage adjustment in renal insufficiency Combivir®, Trizivir® not for patients with CrCl <50mL/min	Minimal toxicity Lactic acidosis with hepatic steatosis (rare but potentially life-threatening toxicity with use of NRTIs)

GENERIC NAME (ABBREVIATION)/TRADE NAME	FORMULATION	DOSING RECOMMENDATIONS	FOOD EFFECT	ORAL BIO- AVAIL- ABILITY	SERUM HALF- LIFE	INTRA- CELLULAR HALF-LIFE	ELIMINATION	ADVERSE EVENTS
<b>Stavudine (d4T)</b> Zerit®	<u>Zerit®</u> : 15, 20, 30, 40mg capsules or 1mg/mL for oral solution	<u>Body Weight &gt;60 kg:</u> 40mg b.i.d; <u>Body Weight &lt;60 kg:</u> 30mg b.i.d	Take without regard to meals	86%	1.0 hour	7.5 hours	Renal excretion 50%  Dosage adjustment in renal insufficiency	Peripheral neuropathy  Lipodystrophy  Rapidly progressive ascending neuromuscular weakness (rare)  Pancreatitis  Lactic acidosis with hepatic steatosis (higher incidence with d4T than with other NRTIs)  Hyperlipidaemia
<b>Tenofovir Disoproxil Fumarate (TDF)</b> Viread®, Truvada® (w/FTC)	<u>Viread®</u> : 300mg tablet <u>Truvada®</u> : TDF, 300mg + FTC, 200mg	<u>Viread®</u> : 1 tablet q.d <u>Truvada®</u> : 1 tablet q.d	Take without regard to meals	25% in fasting state; 39% with high-fat meal	17 hours	>60 hours	Renal excretion  Dosage adjustment in renal insufficiency  Truvada® not for patients with CrCl <30mL/min	Asthenia, headache, diarrhoea, nausea, vomiting, and flatulence  Renal insufficiency  Lactic acidosis with hepatic steatosis (rare but potentially life-threatening toxicity with use of NRTIs)

GENERIC NAME (ABBREVIATION)/TRADE NAME	FORMULATION	DOSING RECOMMENDATIONS	FOOD EFFECT	ORAL BIO- AVAIL- ABILITY	SERUM HALF- LIFE	INTRA- CELLULAR HALF-LIFE	ELIMINATION	ADVERSE EVENTS
<b>Zalcitabine (ddC)</b> Hivid <sup>®</sup>	0.375, 0.75mg tablets	0.75mg t.i.d	Take without regard to meals	85%	1.2 hours	N/A	Renal excretion 70%  Dosage adjustment in renal insufficiency	Peripheral neuropathy  Stomatitis  Lactic acidosis with hepatic steatosis (rare but potentially life-threatening toxicity with use of NRTIs)  Pancreatitis
<b>Zidovudine (AZT, ZDV)</b> Retrovir <sup>®</sup> ; Combivir <sup>®</sup> (w/3TC); Trizivir <sup>®</sup> (w/3TC + ABC)	<u>Retrovir<sup>®</sup></u> : 100mg capsules, 300mg tablets, 10mg/mL intravenous solution, 10mg/mL oral solution  <u>Combivir<sup>®</sup></u> : 3TC, 150mg + ZDV, 300mg  <u>Trizivir<sup>®</sup></u> : 3TC, 150mg + ZDV, 300mg + ABC, 300mg	<u>Retrovir<sup>®</sup></u> : 300mg b.i.d <b>OR</b> 200mg t.i.d  <u>Combivir<sup>®</sup></u> or <u>Trizivir<sup>®</sup></u> : 1 tablet b.i.d	Take without regard to meals	60%	1.1 hours	7 hours	Metabolised to AZT glucuronide (GAZT)  Renal excretion of GAZT  Dosage adjustment in renal insufficiency  Combivir <sup>®</sup> , Trizivir <sup>®</sup> not for patients with CrCl <50mL/min	Bone marrow suppression: macrocytic anaemia or neutropaenia  Gastrointestinal intolerance, headache, insomnia, asthaenia  Lactic acidosis with hepatic steatosis (rare but potentially life-threatening toxicity associated with use of NRTIs)

**Table 12: Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)**

GENERIC NAME (ABBREVIATION)/TRADE NAME	FORM	DOSING RECOMMENDATIONS	FOOD EFFECT	ORAL BIO-AVAILABILITY	SERUM HALF-LIFE	ELIMINATION	ADVERSE EVENTS
<b>Delavirdine (DLV)</b> Rescriptor®	100mg tablets or 200mg tablets	400mg t.i.d  4 100mg tablets can be dispersed in >3 ounces of water to produce slurry  200mg tablets should be taken as intact tablets  Separate dosing from buffered ddi or antacids by 1 hour	Take without regard to meals	85%	5.8 hours	Metabolised by cytochrome P450 (3A inhibitor)  51% excreted in urine (<5% unchanged)  44% in faeces	Rash*  Increased transaminase levels  Headaches
<b>Efavirenz (EFV)</b> Sustiva®	50, 100, 200mg capsules or 600mg tablets	600mg q.d on an empty stomach, at or before bedtime	High-fat/high-caloric meals increase peak plasma concentrations of capsules by 39% and tablets by 79%  Take on an empty stomach	Data not available	40-55 hours	Metabolised by cytochrome P450 (3A mixed inducer/inhibitor)  14%-34% excreted in urine (glucuronidated metabolites, <1% unchanged)  16%-61% in faeces	Rash*  CNS symptoms†  Increased transaminase levels  False-positive cannabinoid test  Teratogenic in monkeys‡
<b>Nevirapine (NVP)</b> Viramune®	200mg tablets or 50mg/5mL oral suspension	200mg q.d for 14 days; thereafter, 200mg po b.i.d	Take without regard to meals	>90%	25-30 hours	Metabolised by cytochrome P450 (3A inducer)  80% excreted in urine (glucuronidated metabolites; <5% unchanged)  10% in faeces	Rash including Stevens-Johnson syndrome*  Symptomatic hepatitis, including fatal hepatic necrosis, have been reported‡

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\*During clinical trials, NNRTIs were discontinued because of rash among 7% of patients taking NVP, 4.3% of patients taking DLV, and 1.7% of patients taking EFV. Rare cases of Stevens-Johnson syndrome have been reported with the use of all three NNRTIs, the highest incidence seen with NVP use.

†Adverse events can include dizziness, somnolence, insomnia, abnormal dreams, confusion, abnormal thinking, impaired concentration, amnesia, agitation, depersonalisation, hallucinations, and euphoria. Overall frequency of any of these symptoms associated with use of EFV was 52%, as compared with 26% among control subjects; 2.6% of those persons on EFV discontinued the drug because of these symptoms. Symptoms usually subside spontaneously after 2-4 weeks.

‡Symptomatic hepatic events (accompanied by rash in approximately 50% of cases) occur in significantly higher frequency in female patients with pre-NVP CD4+ T cell counts of  $>250$  cells/mm<sup>3</sup> or in male patients with pre-NVP CD4+ T cell counts of  $>400$  cells/mm<sup>3</sup>.

**Table 13: Protease Inhibitors (PIs)**

GENERIC NAME/TRADE NAME	FORM	DOSING RECOMMENDATIONS	FOOD EFFECT	ORAL BIO-AVAILABILITY	SERUM HALF-LIFE	ROUTE OF METABOLISM	STORAGE	ADVERSE EVENTS
<p><b>Amprenavir (APV)</b> Agenerase®</p>	<p>50mg capsules 15mg/mL oral solution (Capsules and solution NOT inter-changeable on mg per mg basis)</p>	<p>1,400mg b.i.d (oral solution) <b>Note:</b> APV and RTV oral solution should not be co-administered due to competition of the metabolic pathway of the 2 vehicles <b>Note:</b> APV, 150mg capsule is no longer available; consider using f-APV in these patients</p>	<p>High-fat meal decreases blood concentration 21%; can be taken with or without food, but high-fat meals should be avoided</p>	<p>Not determined in humans</p>	<p>7.1-10.6 hours</p>	<p>Cytochrome P450 3A4 inhibitor inducer, and substrate  Dosage adjustment in hepatic insufficiency recommended</p>	<p>Room temperature (up to 25°C or 77°F)</p>	<p>GI intolerance, nausea, vomiting, diarrhoea Rash Oral paresthaesias Hyperlipidaemia Transaminase elevation Hyperglycaemia Fat maldistribution Possible increased bleeding episodes in patients with haemophilia <b>Note:</b> Oral solution contains propylene glycol; contraindicated in pregnant women, children age &lt;4 years, patients with hepatic or renal failure, and patients treated with disulfiram or metronidazole</p>

GENERIC NAME/TRADE NAME	FORM	DOSING RECOMMENDATIONS	FOOD EFFECT	ORAL BIO-AVAILABILITY	SERUM HALF-LIFE	ROUTE OF METABOLISM	STORAGE	ADVERSE EVENTS
<b>Atazanavir (ATV)</b> Reyataz™	100, 150, 200mg capsules	400mg q.d <u>If Taken with EFV (or TDF):</u> RTV, 100mg + ATV, 300mg q.d	Administration with food increases bioavailability  Take with food; avoid taking with antacids	Not determined	7 hours	Cytochrome P450 3A4 inhibitor and substrate  Dosage adjustment in hepatic insufficiency recommended	Room temperature (up to 25°C or 77°F)	Indirect hyperbilirubinaemia  Prolong PR interval—some patients experienced asymptomatic 1 <sup>st</sup> -degree AV block  Use with caution in patients with underlying condition defects or on concomitant medications that can cause PR prolongation  Hyperglycaemia  Fat maldistribution  Possible increased bleeding episodes in patients with haemophilia

GENERIC NAME/TRADE NAME	FORM	DOSING RECOMMENDATIONS	FOOD EFFECT	ORAL BIO-AVAILABILITY	SERUM HALF-LIFE	ROUTE OF METABOLISM	STORAGE	ADVERSE EVENTS
<b>fos-amprenavir (f-APV)</b> Lexiva™	700mg tablet	<u>ARV-Naïve Patients:</u> f-APV 1,400mg b.i.d; <b>OR</b> (f-APV, 1,400mg + RTV, 200mg) q.d; <b>OR</b> (f-APV, 700mg + RTV, 100mg) b.i.d <u>PI-Experienced Patients (once-daily regimen not recommended):</u> (f-APV, 700mg + RTV, 100mg) b.i.d <u>Co-Administration with EFV (unboosted f-APV not recommended):</u> (f-APV, 700mg + RTV 100mg) b.i.d; <b>OR</b> (f-APV, 1,400mg + RTV, 300mg) q.d	No significant change in APV pharmacokinetics in fed or fasting state	Not established	7.7 hours (amprenavir)	Amprenavir is a cytochrome P450 3A4 inhibitor, inducer, and substrate  Dosage adjustment in hepatic insufficiency recommended	Room temperature (up to 25°C or 77°F)	Skin rash (19%) Diarrhoea, nausea, vomiting Headache Transaminase elevation Hyperglycaemia Fat maldistribution and lipid abnormalities Possible increased bleeding episodes in patients with haemophilia

GENERIC NAME/TRADE NAME	FORM	DOSING RECOMMENDATIONS	FOOD EFFECT	ORAL BIO-AVAILABILITY	SERUM HALF-LIFE	ROUTE OF METABOLISM	STORAGE	ADVERSE EVENTS
<b>Indinavir (IDV)</b> Crixivan®	200, 333, 400mg capsules	800mg q8h <u>With RTV:</u> [IDV, 800mg + RTV, 100mg or 200mg] q12h	<u>For Unboosted IDV:</u> Levels decrease by 77%  Take 1 hour before or 2 hours after meals; may take with skim milk or low-fat meal  <u>For RTV-Boosted IDV:</u> Take with or without food	65%	1.5-2 hours	Cytochrome P450 (3A4 inhibitor; less than RTV)  Dosage adjustment in hepatic insufficiency recommended	Room temperature 15-30°C (59-86°F), protect from moisture	Nephro-lithiasis  GI intolerance, nausea  Indirect hyperbilirubinaemia  Misc.: headache, asthaenia, blurred vision, dizziness, rash, metallic taste, thrombocytopaenia, alopecia, and haemolytic anaemia  Hyperglycaemia  Fat redistribution  Possible increased bleeding episodes in patients with haemophilia
<b>Lopinavir + Ritonavir (LPV/r)</b> Kaletra®	Each capsule contains LPV, 133.3mg + RTV, 33.3mg  <u>Oral Solution:</u> Each 5mL contains	LPV, 400mg + RTV, 100mg (3 capsules or 5mL) b.i.d  <u>With EFV or NVP:</u> [LPV, 533mg + RTV, 133mg] (4	Moderate fat meal increases AUC of capsules and solution by 48% and 80%,	Not determined in humans	5-6 hours	Cytochrome P450 (3A4 inhibitor and substrate)	Refrigerated capsules and solution are stable until date on label if stored at	GI intolerance, nausea, vomiting, diarrhoea  Asthaenia  Hyperlipidaemia (esp.

GENERIC NAME/TRADE NAME	FORM	DOSING RECOMMENDATIONS	FOOD EFFECT	ORAL BIO-AVAILABILITY	SERUM HALF-LIFE	ROUTE OF METABOLISM	STORAGE	ADVERSE EVENTS
	LPV, 400mg + RTV, 100mg <b>Note:</b> Oral solution contains 42% alcohol	capsules or 6.7mL) b.i.d	respectively Take with food				room temperature (up to 25°C or 77°F) stable for 2 months	hypertriglyceridaemia) Elevated serum trans-aminases Hyperglycaemia Fat maldistribution Possible increased bleeding episodes in patients with haemophilia
<b>Nelfinavir (NFV)</b> Viracept®	250mg tablets 625mg tablets 50mg/g oral powder	1,250mg b.i.d <b>OR</b> 750mg t.i.d	Levels increase 2-3 fold Take with meal or snack	20-80%	3.5-5 hours	Cytochrome P450 3A4 inhibitor and substrate	Room temperature 15-30°C (59-86°F)	Diarrhoea; Hyperlipidaemia Hyperglycaemia Fat redistribution Possible increased bleeding episodes in patients with haemophilia Serum transaminase elevation

GENERIC NAME/TRADE NAME	FORM	DOSING RECOMMENDATIONS	FOOD EFFECT	ORAL BIO-AVAILABILITY	SERUM HALF-LIFE	ROUTE OF METABOLISM	STORAGE	ADVERSE EVENTS
<b>Ritonavir (RTV)</b> Norvir®	100mg capsules OR 600mg/7.5mL solution	600mg q12h* (when RTV is used as sole PI)  <u>As Pharmacokinetic Booster for Other PIs:</u> 100mg-400mg/day in 1-2 divided doses	Levels increase by 15%  Take with food if possible; this may improve tolerability	Not determined	3-5 hours	Cytochrome P450 (3A4>2D6; potent 3A4 inhibitor)	Refrigerate capsules  Capsules can be left at room temperature (up to 25°C or 77°F) for ≤30 days;  Oral solution should NOT be refrigerated	GI intolerance, nausea, vomiting, diarrhoea;  Paresthesias: circumoral and extremities  Hyperlipidaemia, esp. hypertriglyceridaemia  Hepatitis  Asthaenia  Taste perversion  Hyperglycaemia  Fat maldistribution  Possible increased bleeding episodes in patients with haemophilia

GENERIC NAME/TRADE NAME	FORM	DOSING RECOMMENDATIONS	FOOD EFFECT	ORAL BIO-AVAILABILITY	SERUM HALF-LIFE	ROUTE OF METABOLISM	STORAGE	ADVERSE EVENTS
<b>Saquinavir</b> tablets and hard gel capsules <b>(SQV)</b> Invirase®	200mg capsules 500mg tablets	Unboosted SQV -not recommended <u>With RTV:</u> (RTV, 100mg + SQV, 1,000mg) b.i.d	Take within 2 hours of a meal when taken with RTV	4% erratic (when taken as sole PI)	1-2 hours	Cytochrome P450 (3A4 inhibitor and substrate)	Room temperature 15-30°C (59-86°F)	GI intolerance, nausea and diarrhoea Headache Elevated transaminase enzymes Hyperlipidaemia Hyperglycaemia Fat redistribution Possible increased bleeding episodes in patients with haemophilia
<b>Saquinavir</b> soft gel capsule <b>(SQV-sgc)</b> Fortovase®	200mg capsules	<u>Unboosted SQV-sgc:</u> 1,200mg t.i.d <u>With RTV:</u> (RTV, 100mg + SQV-sgc, 1,000mg) b.i.d	Levels increase 6-fold  Take with or up to 2 hours after a meal as sole PI or with RTV	Not determined	1-2 hours	Cytochrome P450 (3A4 inhibitor; less than RTV)	Refrigerate or store at room temperature ≤25°C (77°F) for up to 3 months	GI intolerance, nausea, diarrhoea, abdominal pain, and dyspepsia Headache Hyperlipidaemia Elevated transaminase enzymes Hyper-glycaemia Fat maldistribution Possible increased bleeding episodes in patients with haemophilia

**\*Dose Escalation for RTV When Used as Sole PI:** Days 1 and 2: 300mg 2x; day 3-5: 400mg 2x; day 6-13: 500mg 2x; day 14: 600mg 2x

**Table 14: Fusion Inhibitors**

GENERIC NAME/TRADE NAME	FORM	DOSING RECOMMENDATIONS	BIO-AVAILABILITY	SERUM HALF-LIFE	ROUTE OF METABOLISM	STORAGE	ADVERSE EVENTS
<b>Enfuvirtide (T20)</b> Fuzeon™	<p><u>Injectable:</u> In lyophilised powder</p> <p>Each single-use vial contains 108mg of enfuvirtide to be reconstituted with 1.1mL of sterile water for injection for delivery of approximately 90mg/1mL</p>	90mg (1mL) SC b.i.d	84.3% (SC compared to IV)	3.8 hours	Expected to undergo catabolism to its constituent amino acids, with subsequent recycling of the amino acids in the body pool	<p>Store at room temperature (up to 25°C or 77°F)</p> <p>Reconstituted solution should be stored under refrigeration at 2°C to 8°C (36°F to 46°F) and used within 24 hours</p>	<p><u>Local Injection Site Reactions:</u> Almost 100% of patients (pain, erythema, induration, nodules and cysts, pruritus, ecchymosis)</p> <p>Increased rate of bacterial pneumonia</p> <p><u>Hypersensitivity Reaction (&lt;1%):</u> Symptoms may include rash, fever, nausea, vomiting, chills, rigors, hypotension, or elevated serum transaminases; rechallenge is not recommended</p>

**APPENDIX B: DRUG-DRUG INTERACTIONS BETWEEN PIs AND NNRTIS**

PIs and NNRTIs are potent inhibitors and inducers of the cytochrome P450 (CYP450) enzymes in the liver, which are responsible for the metabolism of these agents. For this reason, significant drug-drug interactions between PIs are common. Dosing adjustments are often necessary when two or more PIs and/or NNRTIs are administered concurrently in an ARV regimen, as detailed in the tables below.

**Table 15: Interactions between PIs**

RTV is a potent inhibitor of the CYP450 system. RTV-mediated inhibition of the hepatic metabolism of other PIs can and often is used to therapeutic advantage. When administered at low doses (e.g. 100-200mg once or twice daily), this agent will significantly boost the serum levels of a co-administered PI, resulting in improved serum pharmacokinetics and higher clinical efficacy. Many PIs (e.g. IDV, SQV, LPV, APV, ATV) are therefore commonly co-administered with low doses of RTV, as detailed in the table below.

DRUG AFFECTED	RITONAVIR (RTV)	SAQUINAVIR (SQV)*	NELFINAVIR (NFV)	AMPRENAVIR (APV)	LOPINAVIR/RITONAVIR (LPV/R)	ATAZANAVIR (ATV)
<b>PIs</b>						
<b>Indinavir (IDV)</b>	<u>Levels:</u> IDV increase 2-5x. <u>Dose:</u> 400/400mg or 800/100mg or 800/200mg IDV/RTV b.i.d. <b>Caution: Renal events may be increased with higher IDV concentrations.</b>	<u>Levels:</u> IDV no effect. SQV increase 4-7x. <u>Dose:</u> Insufficient data.	<u>Levels:</u> IDV increase 50%; NFV increase 80%. <u>Dose:</u> Limited data for IDV 1,200mg b.i.d + NFV 1,250mg b.i.d.	<u>Levels:</u> APV AUC increase 33%. <u>Dose:</u> No change.	<u>Levels:</u> IDV AUC and C <sub>min</sub> increased. <u>Dose:</u> IDV 600mg b.i.d.	Co-administration of these agents is not recommended because of potential for additive hyperbilirubinaemia.
<b>Ritonavir (RTV)</b>		<u>Levels:</u> RTV no effect. SQV increase 20x <sup>†‡</sup> . <u>Dose:</u> 1,000/100mg SQV sgc or hgc/RTV b.i.d or 400/400mg b.i.d.	<u>Levels:</u> RTV no effect; NFV increase 1.5x. <u>Dose:</u> RTV 400mg b.i.d + NFV 500-750mg b.i.d.	<u>Levels:</u> APV AUC increase 2.5–3.5x. <u>Dose:</u> 600/100mg APV/RTV b.i.d. or 1,200/200mg APV/RTV q.d	LPV is co-formulated with RTV as Kaletra™.	ATV/r 300/100 increase ATV AUC by 238%.

DRUG AFFECTED	RITONAVIR (RTV)	SAQUINAVIR (SQV)*	NELFINAVIR (NFV)	AMPRENAVIR (APV)	LOPINAVIR/RITONAVIR (LPV/R)	ATAZANAVIR (ATV)
Saquinavir (SQV)			<u>Levels:</u> SQV increase 3-5x; NFV increase 20% <sup>†</sup> . <u>Dose:</u> Standard NFV; Fortovase <sup>®</sup> , 800mg t.i.d or 1,200mg b.i.d.	<u>Levels:</u> APV AUC decrease 32%. <u>Dose:</u> Insufficient data.	<u>Levels:</u> SQV <sup>†</sup> AUC and Cmin increased. <u>Dose:</u> SQV 1,000mg b.i.d, LPV/r standard.	SQV 1,200 mg q.d + ATV 400 q.d; increase SQV AUC by 449%, no formal recommendation.
Nelfinavir (NFV)				<u>Levels:</u> APV AUC increase 1.5x. <u>Dose:</u> Insufficient data.	<u>Levels:</u> LPV decrease 27%; NFV increase 25%. <u>Dose:</u> Insufficient data.	
Amprenavir (APV)					APV: AUC and Cmin increased relative to APV without RTV; APV, AUC, and Cmin are reduced relative to APV + RTV; LPV Cmin may be decreased relative to LPV/r. <u>Dose:</u> APV 600-750mg b.i.d; LPV/r standard or consider dose increase to 533/133mg b.i.d; consider monitoring PI concentrations.	
Lopinavir/Ritonavir (LPV/r)						No information with LPV/ATV; RTV 100mg increases ATV AUC 238%.

\*Several drug interaction studies have been completed with SQV given as Invirase<sup>®</sup> or Fortovase<sup>®</sup>. Results from studies conducted with Invirase<sup>®</sup> may not be applicable to Fortovase<sup>®</sup>.

<sup>†</sup>Study conducted with Fortovase<sup>®</sup>.

<sup>‡</sup>Study conducted with Invirase<sup>®</sup>.

**Table 16: Interactions between PIs and NNRTIs**

DRUG AFFECTED	NEVIRAPINE (NVP)	DELAVIRDINE (DLV)	EFAVIRENZ (EFV)
<b>PIs and NNRTIs</b>			
<b>Indinavir (IDV)</b>	<u>Levels:</u> IDV decrease 28%; NVP no effect. <u>Dose:</u> IDV 1,000mg q8h or consider IDV/RTV, NVP standard.	<u>Levels:</u> IDV increase >40%; DLV no effect. <u>Dose:</u> IDV 600mg q8h. DLV: standard.	<u>Levels:</u> IDV decrease 31%. <u>Dose:</u> IDV 1.000mg q8h or consider IDV/RTV, EFV standard.
<b>Ritonavir (RTV)</b>	<u>Levels:</u> RTV decrease 11%; NVP no effect. <u>Dose:</u> Standard.	<u>Levels:</u> RTV increase 70%. DLV: no effect. <u>Dose:</u> DLV: standard. RTV: no data.	<u>Levels:</u> RTV increase 18%. EFV increase 21%. <u>Dose:</u> Standard.
<b>Saquinavir (SQV)</b>	<u>Levels:</u> SQV decrease 25%. NVP no effect. <u>Dose:</u> Consider SQV/RTV.	<u>Levels:</u> SQV <sup>‡</sup> increase 5 times; DLV no effect. <u>Dose:</u> Fortovase <sup>®</sup> 800mg t.i.d, DLV standard (monitor transaminase levels).	<u>Levels:</u> SQV <sup>‡</sup> decrease 62%. EFV decrease 12%. SQV is not recommended to be used as sole PI when EFV is used. <u>Dose:</u> Consider SQV/RTV.
<b>Nelfinavir (NFV)</b>	<u>Levels:</u> NFV increase 10%. NVP no effect. <u>Dose:</u> Standard.	<u>Levels:</u> NFV increase 2 times; DLV decrease 50%. <u>Dose:</u> No data (monitor for neutropaenic complications).	<u>Levels:</u> NFV increase 20%. <u>Dose:</u> Standard.
<b>Amprenavir (APV)</b>	No data.	<u>Levels:</u> APV AUC increase 130%. DLV AUC decrease 61%. <u>Dose:</u> No data.	<u>Levels:</u> APV AUC decrease 36%. <u>Dose:</u> Administer APV/RTV with EFV, EFV standard.
<b>Lopinavir/Ritonavir (LPV/r)</b>	<u>Levels:</u> LPV Cmin decrease 55%. <u>Dose:</u> Consider LPV/r 533/133mg b.i.d in PI-experienced patients; NVP standard.	<u>Levels:</u> LPV levels expected to increase. <u>Dose:</u> Insufficient data.	<u>Levels:</u> LPV AUC decrease 40%; EFV no change. <u>Dose:</u> Consider LPV/r 533/133mg b.i.d. EFV standard.
<b>Atazanavir (ATV)</b>	No data. A decrease in ATV levels is expected.	No data.	<u>Levels:</u> ATV AUC decrease 74%, EFV no change. <u>Dose:</u> Recommend ATV 300 + RTV 100mg each given q.d with food; EFV standard.
<b>Nevirapine (NVP)</b>		No data.	<u>Levels:</u> NVP: no effect. EFV: AUC decrease 22%.
<b>Delavirdine (DLV)</b>	No data.		No data.

<sup>‡</sup>Study conducted with Invirase<sup>®</sup>.

APPENDIX C: DRUG INTERACTIONS BETWEEN ARVs AND OTHER DRUGS

Table 17: Drug Interactions between ARVs and Other Drugs

DRUG INTERACTIONS REQUIRING DOSE MODIFICATIONS OR CAUTIOUS USE			
Drugs Affected	Indinavir (IDV)	Ritonavir* (RTV)	Saquinavir† (SQV)
<b>ANTIFUNGALS</b>			
<b>Ketoconazole</b>	<u>Levels:</u> IDV ↑ 68%. <u>Dose:</u> IDV 600mg t.i.d.	<u>Levels:</u> Ketoconazole ↑ 3x. <u>Dose:</u> Use with caution; do not exceed 200mg ketoconazole daily.	<u>Levels:</u> SQV ↑ 3x. <u>Dose:</u> If ketoconazole dose is >200mg/day, monitor for excessive diarrhoea, nausea, and abdominal discomfort; adjust doses accordingly.
<b>Voriconazole</b>	<u>Levels:</u> No significant changes in AUC of azole or IDV (healthy subjects). <u>Dose:</u> Standard.	No data, but potential for bi-directional inhibition between voriconazole and PIs; monitor for toxicities.	No data, but potential for bi-directional inhibition between voriconazole and PIs; monitor for toxicities.
<b>ANTIMYCOBACTERIALS</b>			
<b>Rifampin (RIF)<sup>2</sup></b>	<u>Levels:</u> IDV ↓ 89%. <b>Contra-indicated.</b>	<u>Levels:</u> RTV ↓ 35%. <u>Dose:</u> No data; increased liver toxicity possible.	<u>Levels:</u> SQV ↓ 84%. <b>Contra-indicated</b> , unless using RTV + SQV, then use RIF 600mg q.d or t.i.w.
<b>Rifabutin</b>	<u>Levels:</u> IDV ↓ 32%. Rifabutin ↑ 2x. <u>Dose:</u> ↓ rifabutin to 150mg q.d or 300mg t.i.w. IDV 1,000mg t.i.d.	<u>Levels:</u> Rifabutin ↑ 4x. <u>Dose:</u> ↓ rifabutin to 150mg q.o.d. or dose t.i.w. RTV: Standard.	<u>Levels:</u> SQV ↓ 40%. No rifabutin dose adjustment unless using RTV + SQV, then use rifabutin 150mg t.i.w.
<b>Clarithromycin</b>	<u>Levels:</u> Clarithromycin ↑ 53%. No dose adjustment.	<u>Levels:</u> Clarithromycin ↑ 77%. <u>Dose:</u> Adjust clarithromycin dose for moderate and severe renal impairment.	<u>Levels:</u> Clarithromycin ↑ 45%. SQV ↑ 177%. No dose adjustment.
<b>ORAL CONTRACEPTIVES</b>			
	<u>Levels:</u> Norethindrone ↑ 26%; ethinylestradiol ↑ 24%. No dose adjustment.	<u>Levels:</u> Ethinyl estradiol ↓ 40%. Use alternative or additional method.	No data.
<b>LIPID-LOWERING AGENTS</b>			
<b>Simvastatin Lovastatin</b>	<u>Levels:</u> Potential for large increase in statin levels. <b>Avoid concomitant use.</b>	<u>Levels:</u> Potential for large increase in statin levels. <b>Avoid concomitant use.</b>	<u>Levels:</u> Potential for large increase in statin levels. <b>Avoid concomitant use.</b>

<b>Atorvastatin</b>	Levels: Potential for increase in AUC. Use lowest possible starting dose of atorvastatin with careful monitoring.	Levels: 450% ↑ when administered with SQV/RTV combination. Use lowest possible starting dose of atorvastatin with careful monitoring.	Levels: 450% ↑ when administered with SQV/RTV combination. Use lowest possible starting dose of atorvastatin with careful monitoring.
<b>Pravastatin</b>	No data.	Levels: 50% ↓ when administered with SQV/RTV combination. No dose adjustment needed.	Levels: 50% ↓ when administered with SQV/RTV combination. No dose adjustment needed.
<b>ANTICONVULSANTS</b>			
<b>Carbamazepine</b> <b>Phenobarbital</b> <b>Phenytoin</b>	Carbamazepine markedly ↓ IDV AUC. <b>Consider alternative agent.</b>	Carbamazepine: ↑ serum levels when co-administered with RTV; use with caution; monitor anticonvulsant levels.	Unknown, but may markedly ↓ SQV levels. Monitor anticonvulsant levels.
<b>METHADONE</b>			
	No change in methadone levels.	Methadone ↓ 37%. Monitor and titrate dose if needed. May require ↑ methadone dose.	No data.
<b>ERECTILE DYSFUNCTION AGENTS</b>			
<b>Sildenafil</b>	Sildenafil AUC ↑ 3x. Use cautiously. Start with reduced dose of 25mg q48h and monitor for adverse effects.	Sildenafil AUC ↑ 11x. Use cautiously. Start with reduced dose of 25mg q48h and monitor for adverse effects.	Sildenafil AUC ↑ 2x. Use a 25mg starting dose of sildenafil.
<b>Vardenafil</b>	Vardenafil AUC ↑ 16x. Start with a 2.5mg dose and do not exceed a single 2.5mg dose in 24 hours. Do not exceed 2.5mg in 72 hours if administered with RTV.	Vardenafil AUC ↑ 49x. Start with a 2.5mg dose, and do not exceed a single 2.5mg dose in 72 hours.	No data, but vardenafil AUC may be substantially increased. Start with a 2.5mg dose and do not exceed a single 2.5mg dose in 24 hours. Do not exceed a single 2.5mg dose in 72 hours if administered with RTV.
<b>MISCELLANEOUS</b>			
	Grapefruit juice ↓ IDV levels by 26%.	<b>Many possible interactions.</b> Desipramine ↑ 145%, reduce dose. Theophylline ↓ 47%, monitor theophylline levels.	Grapefruit juice ↑ SQV levels. Dexamethasone ↓ SQV levels.

\*Drugs for which plasma concentrations may be decreased by co-administration with RTV: anticoagulants (warfarin), anticonvulsants (phenytoin, divaproex, lamotrigine), antiparasitics (atovaquone).

†Some drug interaction studies were conducted with Invirase®. May not necessarily apply to use with Fortovase®.

ΣThere are limited data on RTV-SQV and RTV-LPV demonstrating that RTV compensates for RIF induction. In one small study, higher-boosting doses of RTV (up to 400mg per dose) or an increased dose of LPV/RTV 800/200mg were needed to fully offset RIF-inducing activity of LPV. Of note, 28% of subjects discontinued due to increases in LFTs. The safety of this combination is still under evaluation. Whether RTV can be used to offset RIF induction of all other PIs, or whether this therapeutic manoeuvre is more broadly applicable, requires further study.

(Adapted from: US DHHS. Table 20: Drug Interactions Between Antiretrovirals and Other Drugs: PIs, NNRTIs, and NRTIs in Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. 2003. Available at: <http://AIDSinfo.nih.gov/guidelines>. Accessed 2003)

**APPENDIX D: DRUGS THAT SHOULD NOT BE USED IN COMBINATION WITH PIs OR NNRTIS DUE TO DANGEROUS DRUG INTERACTIONS**

	<b>Drug Category<sup>‡</sup></b>	<b>Calcium Channel Blocker</b>	<b>Cardiac</b>	<b>Lipid-Lowering Agents</b>	<b>Antimycobacterial<sup>‡</sup></b>	<b>Anti-histamine<sup>‡</sup></b>	<b>Gastro-intestinal Drugs<sup>‡</sup></b>	<b>Neuroleptic</b>	<b>Psychotropic</b>	<b>Ergot Alkaloids (vasoconstrictor)</b>	<b>Herbs</b>	<b>Other</b>
<b>PIs</b>	<b>Indinavir (IDV)</b>	(none)	(none)	simvastatin lovastatin	RIF rifapentine	astemizole terfenadine	cisapride	pimozide	midazolam <sup>‡</sup> triazolam	dihydroergotamine (D.H.E. 45) ergotamine <sup>†</sup> (various forms) ergonovine methylergonovine	St. John's wort	ATV
	<b>Ritonavir (RTV)</b>	bepridil	amiodarone flecainide propafenone quinidine	simvastatin lovastatin	rifapentine	astemizole terfenadine	cisapride	pimozide	midazolam <sup>‡</sup> triazolam	dihydroergotamine (D.H.E. 45) ergotamine <sup>†</sup> (various forms) ergonovine methylergonovine	St. John's wort	
	<b>Saquinavir (SQV)</b>	(none)	(none)	simvastatin lovastatin	RIF <sup>Δ</sup> rifabutin <sup>Δ</sup> rifapentine	astemizole terfenadine	cisapride	pimozide	midazolam <sup>‡</sup> triazolam	dihydroergotamine (D.H.E. 45) ergotamine <sup>†</sup> (various forms) ergonovine methylergonovine	St. John's wort	
	<b>Nelfinavir (NFV)</b>	(none)	(none)	simvastatin lovastatin	RIF rifapentine	astemizole terfenadine	cisapride	pimozide	midazolam <sup>‡</sup> triazolam	dihydroergotamine (D.H.E. 45) ergotamine <sup>†</sup> (various forms) ergonovine methylergonovine	St. John's wort	
	<b>Amprenavir (APV)<sup>*</sup></b>	bepridil	(none)	simvastatin lovastatin	RIF rifapentine	astemizole terfenadine	cisapride	pimozide	midazolam <sup>‡</sup> triazolam	dihydroergotamine (D.H.E. 45) ergotamine <sup>†</sup> (various forms) ergonovine methylergonovine	St. John's wort	
	<b>Lopinavir (LPV) + Ritonavir</b>	(none)	flecainide propafenone	simvastatin lovastatin	RIF <sup>‡</sup> rifapentine	astemizole terfenadine	cisapride	pimozide	midazolam <sup>‡</sup> triazolam	dihydroergotamine (D.H.E. 45) ergotamine <sup>†</sup> (various forms) ergonovine methylergonovine	St. John's wort	

**NNRTIs**

Drug Category <sup>#</sup>	Calcium Channel Blocker	Cardiac	Lipid-Lowering Agents	Antimycobacterial <sup>‡</sup>	Anti-histamine <sup>£</sup>	Gastro-intestinal Drugs <sup>£</sup>	Neuroleptic	Psychotropic	Ergot Alkaloids (vasoconstrictor)	Herbs	Other
<b>Atazanavir (ATV)</b>	bepridil	(none)	simvastatin lovastatin	RIF rifapentine	astemizole terfenadine	cisapride proton pump inhibitors	pimozide	midazolam <sup>Ⓢ</sup> triazolam	dihydroergotamine (D.H.E. 45) ergotamine <sup>†</sup> (various forms) ergonovine methylergonovine	St. John's wort	IDV irinotecan
<b>Nevirapine</b>	(none)	(none)	(none)	RIF rifapentine <sup>‡</sup>	(none)	(none)	(none)	(none)	(none)	St. John's wort	
<b>Delavirdine (DLV)</b>	(none)	(none)	simvastatin lovastatin	RIF rifapentin <sup>‡</sup> rifabutin	astemizole terfenadine	cisapride H-2 blockers proton pump inhibitors	(none)	alprazolam midazolam <sup>Ⓢ</sup> triazolam	dihydroergotamine (D.H.E. 45) ergotamine <sup>†</sup> (various forms) ergonovine methylergonovine	St. John's wort	
<b>Efavirenz (EFV)</b>	(none)	(none)	(none)	rifapentine <sup>‡</sup>	astemizole terfenadine	cisapride	(none)	midazolam <sup>Ⓢ</sup> triazolam	dihydroergotamine (D.H.E. 45) ergotamine <sup>†</sup> (various forms) ergonovine methylergonovine	St. John's wort	

(Adapted from: US DHHS. Table 19: *Drugs That Should Not Be Used With PI or NNRTI Antiretrovirals in Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents, 2003. Available at: <http://AIDSinfo.nih.gov/guidelines>. Accessed 2003)*

<sup>#</sup>Certain listed drugs are contra-indicated based on theoretical considerations. Thus, drugs with narrow therapeutic indices and suspected metabolic involvement with P450–3A, 2D6, or unknown pathways are included in this table. Actual interactions may or may not occur among patients.

<sup>‡</sup>HIV patients being treated with rifapentine have a higher rate of TB relapse than those treated with other rifamycin-based regimens; an alternative agent is recommended for this population.

<sup>^</sup>RIF and rifabutin are contra-indicated unless SQV is combined with RTV.

<sup>‡</sup>In one small study, higher doses of RTV or LPV/r offset RIF-inducing activity of LPV. Of note, 28% of subjects discontinued due to increases in LFTs. The safety of this combination is still under evaluation; further studies are needed.

<sup>Σ</sup>Midazolam can be used with caution as a single dose and given in a monitored situation for procedural sedation.

<sup>†</sup>This is likely a class effect.

<sup>o</sup>Astemizole and terfenadine are not marketed in the United States. The manufacturer of cisapride has a limited-access protocol in place for patients meeting specific clinical eligibility criteria.

\*Each 150mg APV Agenerase<sup>®</sup> capsule has 109 IU (International Units) of vitamin E and 1mL of APV oral solution has 46 IU of vitamin E. At FDA approved doses, the daily amount of vitamin E in Agenerase<sup>®</sup> is a 58-fold increase over the federal government's reference daily intake for adults. Patients should be cautioned to avoid supplemental doses of vitamin E. Multivitamin products containing minimal amounts of vitamin E are likely acceptable.

### **Suggested Alternatives**

***Cerivastatin*** (no longer marketed in the United States), ***simvastatin, lovastatin***: pravastatin and fluvastatin have the least potential for drug-drug interactions; atorvastatin should be used with caution, using the lowest possible starting dose and monitoring closely.

***Rifabutin***: clarithromycin, azithromycin (MAI prophylaxis); clarithromycin, azithromycin, ethambutol (EMB) (MAI treatment)

***Astemizole, terfenadine*** (no longer marketed in the United States): desloratadine, loratadine, fexofenadine, cetirizine

***Midazolam, triazolam***: temazepam, lorazepam

**APPENDIX E: BASIC LABORATORY MONITORING FOR RECOMMENDED FIRST-LINE REGIMENS**

This table is meant to serve as a general guide and should not replace clinical judgment for individual patients. Laboratory monitoring is warranted outside of this schedule for any signs or symptoms suggestive of medication-related toxicity. Tolerance of a HAART regimen may reasonably lead to a decreased frequency of laboratory monitoring. HAART should not be withheld in circumstances where scarce resources do not permit laboratory monitoring as suggested below. Detection of abnormalities on laboratory testing should not necessarily lead to automatic discontinuation or modification of the HAART regimen; rather, the results should be interpreted in the context of the patient’s clinical signs and symptoms. Consultation with an expert HIV clinician is suggested.

HAART REGIMEN	LABORATORY TEST	FREQUENCY	STRENGTH OF RECOMMENDATION	REASON
AZT + 3TC + EFV	CD4+ T cell	BL; q4-6m	Highly recommended	Assess response to therapy
	Hgb/CBC	BL; 4 weeks after initiation;	Highly recommended	Potential for AZT-associated anaemia
	Pregnancy	BL; clinician discretion *	Mandatory	Teratogenicity associated with EFV
	AST or LFTs	BL; q3-6m; symptom-directed	Recommended	Potential for EFV-associated liver toxicity
	HIV viral load	BL; q4-6m	Optional but recommended in setting of suspected treatment failure	Assess response to therapy; confirm suspected treatment failure
	Glucose	BL; q6-12m	Recommended	Insulin resistance associated with EFV
	Cholesterol	BL; 3-6 months after initiation of treatment; clinician discretion	Recommended for patients with other risk factors for coronary artery disease	Dyslipidaemia associated with NNRTIs and PIs
BUN/Creatinine	BL; q6-12 months	Recommended		
AZT + 3TC + NVP	CD4+ T cell	BL; q4-6 months	Recommended	Assess response to therapy
	Hgb/CBC	BL; one month after initiation; symptom-directed	Highly recommended	Potential for AZT-associated anaemia
	AST or LFTs	BL; q3-6m; symptom-directed	Highly recommended	Potential for NVP-associated liver toxicity
	HIV viral load	BL; q3-6m	Optional but recommended in setting	Assess response to therapy; confirm

\*Due to its potential for severe teratogenicity, EFV should not be used in women who are pregnant (especially in the first and second trimesters) or in women at risk for pregnancy (e.g. for whom effective contraception cannot be assured).

HAART REGIMEN	LABORATORY TEST	FREQUENCY	STRENGTH OF RECOMMENDATION	REASON
	Pregnancy test	BL; clinician discretion	of suspected treatment failure	suspected treatment failure recommended
d4T + 3TC + EFV	CD4+ T cell	BL; q3-6m	Highly recommended	Assess response to therapy
	Pregnancy	BL; clinician discretion*	Mandatory	Teratogenicity associated with EFV
	AST	BL; q3-6m; symptom-directed	Recommended	Potential for EFV-associated liver toxicity
	HIV viral load	BL; q3-6m	Optional but recommended in setting of suspected treatment failure	Assess response to therapy; confirm suspected treatment failure
	Glucose	BL; q6-12m	Recommended	Insulin resistance associated with EFV
	Cholesterol	BL; 3-6 months after initiation of treatment; clinician discretion	Recommended for patients with other risk factors for coronary artery disease	Dyslipidaemia associated with NNRTIs and PIs
d4T + 3TC + NVP	CD4+ T cell	BL; q3-6m	Recommended	Assess response to therapy
	AST	BL; q3-6m; symptom-directed	Highly recommended	Potential for NVP-associated liver toxicity
	HIV viral load	BL; q3-6m	Optional but recommended in setting of suspected treatment failure	Assess response to therapy; confirm suspected treatment failure

BL = baseline (before starting therapy)

\*Due to its potential for severe teratogenicity, EFV should not be used in women who are pregnant (especially in the first and second trimesters) or in women at risk for pregnancy (e.g. for whom effective contraception cannot be assured).

## APPENDIX F: HIV RESISTANCE

### INTRODUCTION

HIV resistance can be broadly defined as any change in the virus that improves its ability to replicate in the presence of an antiretroviral drug. This resistance is always relative to the wild-type virus and is rarely absolute. In specific terms, HIV resistance is an altered phenotype resulting from a change in a viral genotype and can be measured both *in vitro* and *in vivo*.

*In vivo*, resistance is defined as failure of a drug to maintain viral suppression in a treated individual. This is identified by a rising viral load when available, otherwise by a falling CD4+ T count, and may be associated with phenotypic and/or genotypic evidence of drug resistance.

A more detailed review of HIV resistance, as well as an online algorithm for interpretation of genotypic resistance assays, can be found at <http://hivdb.stanford.edu>.

### RESISTANCE TO NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS (NSRTIS) AND NUCLEOTIDE REVERSE TRANSCRIPTASE INHIBITORS (NRTIS)

The first data suggesting correlation between the emergence of viral resistance and clinical progression was reported by Larder and colleagues\* two years after AZT became available for clinical use.

**AZT, ZDV:** Mutations emerge in a characteristic sequence, with a first single base mutation usually appearing at codon 70. This appearance is temporary as it is typically replaced by a mutant at codon 215. This mutation is commonly followed by the appearance of single base mutations at codons 41, 67, and 219. The mutation at codon 70 may reappear with prolonged AZT treatment, as can a mutation at codon 210. These mutations (M41L, D67N, K70R, L210W, T215Y/F, and K219Q/E) are known as *thymidine analogue mutations* (TAMs) because they confer cross resistance to d4T, another thymidine analogue, as well. Some experts favour the term *nucleoside-associated mutations* (NAMs) because some degree of cross-resistance has been documented between these mutations and all members of the NRTI class.

Mutations at codon 69 and 151 have also been associated with broad resistance to nearly all members of the NRTI class.

**d4T:** in addition to the TAMs and the mutations at codons 69 and 151 described above, mutations at codon 75 may be associated with resistance.

**ddI:** Resistance to ddI is associated with a mutation at codon 74 (L74V) as well as the TAMs and the mutations at codons 69 and 151. In addition, the K65R mutation may be associated with resistance.

**3TC:** *In vitro*, high-level resistance (500- to 1,000-fold) develops rapidly when the virus carries the single mutation M184V/I. This mutation is also observed *in vivo*. Furthermore, insertion at codon 69 is associated with resistance to 3TC.

**ABC:** *In vitro* selection for resistance to ABC has been associated with the TAMs and mutations at codon 184. Insertion mutations at codon 69 are also associated with resistance to ABC.

**TDF:** *In vitro* selection for reduced sensitivity to TDF has been associated with a mutation at codon 65 (K65R). *In vivo*, the mutation K65R has also been documented in patients failing TDF treatment. In addition, multiple TAMs and/or an insertion mutation at codon 69 can result in resistance to TDF.

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\*Larder BA, Darby G, Richman DD. HIV with reduced sensitivity to zidovudine (AZT) isolated during prolonged therapy. *Science* 243:1731-1734; 1989.

As shown in *Table 17*, many mutations of the reverse transcriptase gene elicited by one ARV induce cross-resistance to other NRTIs.

## RESISTANCE TO NNRTIS

Despite their structural differences, all NNRTIs bind to the same site, a hydrophobic pocket of the HIV reverse transcriptase. A single mutation in this region of the enzyme can result in a conformational change that confers high-level resistance. Cross-resistance between NNRTIs is unfortunately very common; resistance to NVP typically confers cross-resistance to EFV, and *vice-versa*.

Mutated codons contributing to resistance to NNRTIs are shown in *Table 19*.

## RESISTANCE TO PIS

***Mutations of at least twenty-five different codons have been implicated in the development of HIV resistance to PIs. There is also a significant degree of cross-resistance among the members of the PI class.***

***SQV:*** Reduced sensitivity to SQV is most often associated with three mutations in the protease gene at codons 48 (G48V), 84 (I84V), and 90 (L90M). Additional mutations at codons 54, 71, 73, 77, and 82 have also been observed in patients receiving SQV. When SQV is administered with RTV, mutations at codons 24, 62, and 90 have been reported in patients failing treatment.

***RTV:*** Resistance to RTV involves multiple mutations, usually at greater than three sites and up to eleven. Resistant viruses generally show mutation at codons 46, 82, 84, and 90, with the mutation at codon 82 appearing first in most patients. Other mutations have been observed in patients at codons 20, 24, 32, 36, 54, 71, 73, and 77.

***IDV:*** Resistance to IDV is very similar to RTV resistance, with multiple mutations required usually at greater than three sites and up to eleven. Mutations at codon 82 or codon 46 (M46I or M46L) are the most commonly seen (with or without other mutations).

***NFV:*** The most common mutations observed *in vivo* are D30N and L90M. D30N occurs more commonly and does not induce cross-resistance with other PIs. Reduction in susceptibility is also displayed by isolates harbouring a mutation at codon 82 in association with other mutations.

***APV:*** A specific mutation at codon 50 induces resistance to APV. Otherwise, up to three mutations at codons 10, 32, 46, 47, 54, 73, 82, 84, and 90 are required to induce resistance to APV. When APV is administered with RTV, up to five of these mutations are needed.

***LPV:*** LPV is co-formulated with RTV, which boosts the serum drug levels of LPV. Multiple mutations in the protease gene are required to generate significant resistance to LPV/RTV, making this a useful agent for initial as well as salvage therapy.

## RESISTANCE TESTING

### TEST METHODS

There are two types of tests: phenotypic and genotypic assays.

#### ***Phenotypic Assays***

*In vitro*, resistance is based on the ability of the virus to grow in the presence of an inhibitor compared with a more susceptible control virus (wild-type).

These assays measure the ability of HIV to replicate at different concentrations of a tested ARV agent. The method involves isolation, amplification, and insertion of the reverse transcriptase (RT) and protease genes from the patient into a backbone laboratory clone by cloning or by recombination. Replication is then monitored at various drug concentrations and compared with a reference. Results are reported as the IC50 (50% inhibitory concentration) for the test strain relative to that of a reference or a wild-type strain.

### ***Genotypic Assays***

The genotype is defined as the nucleotide sequence from which a protein's amino acid sequence can be deduced. This sequence can be compared to a reference wild-type genotype. Any change from the wild-type is usually reported as a change in amino acid at a specific residue (codon) of the protein.

Genotypic assays identify mutations into the RT and protease gene. The methodology is: 1) amplification of the RT and/or protease gene by RT PCR; 2) DNA sequencing of amplicons generated for the dominant species; and 3) reporting of mutations for each gene.

The results of these assays can be obtained in one to two weeks and are reproducible. Limitations are viral load >500 - 1,000 copies/mL and identification of mutations present in >10% - 20% of plasma virions.

Due to the continuous rising of the number of mutations associated with resistance, only assays allowing the complete determination of nucleotides sequences of the RT *and* protease gene should be used.

Commercial kits exist, but many laboratories utilise their own sequencing methods.

### ***Interpretation of Genotypic Assays***

Resistance to ARV drugs is due to complex combinations of mutations in the HIV genes coding for the RT or protease. The interpretation of the mutations observed and of their combinations needs the expertise of the analyst and algorithms regarding each ARV. As the interpretation algorithms are quickly evolving with time, the following links should be consulted:

Table from IAS-USA updated at <<http://www.iasusa.org>>; see also <<http://hivdb.stanford.edu>>.

Table from ANRS updated at <<http://www.hivfrenchresistance.org>>.

**Table 18: Major Mutations Associated with Reduced Susceptibility to NRTIs**

SEQUENCE OF THE REVERSE TRANSCRIPTASE															
Wild Codons	M41	E44	K65	D67	T69		K70	L74	V75	Y115	Q151	M184	L210	T215	K219
<b>MUTATED CODONS ASSOCIATED WITH RESISTANCE TO:</b>															
AZT	L			N		INSERTION AT CODON 69	R				M		W	Y/F/ A/C/D/E/G /H/I/L/N/S/V	Q/E
d4T	L			N		INSERTION AT CODON 69	R		M/S/A/T		M		W	Y/F/ A/C/D/E/G /H/I/L/N/S/V	Q/E
ddI	L			N		INSERTION AT CODON 69	R	V			M		W	Y/F	Q/E
3TC			R			INSERTION AT CODON 69					M	V/I			
ABC	L		R	N		INSERTION AT CODON 69	R	V		F	M	V/I	W	Y/F	
TDF	L	D	R	N	D/N/S	INSERTION AT CODON 69		V					W	Y/F	

**Table 19: Major Mutations Associated with Reduced Susceptibility to NNRTIs**

SEQUENCE OF THE REVERSE TRANSCRIPTASE GENE								
Wild Codons	L100	K101	K103	V106	Y181	Y188	G190	P225
<b>MUTATED CODONS ASSOCIATED WITH RESISTANCE TO:</b>								
EFV	I	E	H/N/S/T	M	C/I	C/L	A/C/E/Q/S/T/V	H
NVP	I	E	H/N/S/T	M/A	C/I	C/H/L	A/C/E/Q/S/T/V	

**Table 20: Major Mutations Associated with Reduced Susceptibility to PIs**

SEQUENCE OF THE PROTEASE GENE																					
Wild Codons	L10	K20	L24	D30	V32	L33	M36	M46	G48	I50	F53	I54	I62	L63	A71	G73	V77	V82	I84	N88	L90
<b>MUTATED CODONS ASSOCIATED WITH RESISTANCE TO:</b>																					
IDV		M/R	I		I		I	I/L				V/L/M/T			V/T	S/A	I	A/F/S/T	A/V		M
SQV			I						V				V					A/F/S/T	A/V		M
NFV	I			N			I	I/L				V/L/M/T					I	A/F/S/T	A/V	S/D	M
RTV		M/R	I		I		I	I/L				V/L/M/T					I	A/F/S/T	A/V		M
APV	F/I/V	M/R								V		V		P				A/F/S/T	A/V		
LPV/r	F/I/V/R	M/R	I			F		I/L		V	L	V/L/M/T		P	I/L/V/T			A/F/S/T	V		M
ATV	F/I/V	I/M/R	I			F/I/V	I/L/V	I/L	V	L		L/V		P	I/L/V/T	A/C/S/T		A/F/S/T	V		M