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The role of nelfinavir (Vira-cept®)

A dramatic price reduction has been announced for Vira-cept®. However, for reasons outlined below, we envisage only authorizing nelfinavir for selected indications.

Nelfinavir is a widely used protease inhibitor (PI) in developed countries. Its popularity relates primarily to the fact that if virological failure occurs, early resistance mutations are unique to nelfinavir allowing other PIs to be used successfully afterwards. This seems to be true of the HIV subtype (strain) prevalent in developed countries, but preliminary data on subtypes prevalent in developing countries suggest that the resistance mutations seen are not unique to nelfinavir, which will result in cross-resistance to other protease inhibitors.

Nelfinavir appears to be safe in pregnancy. A nelfinavir containing regimen could be used for prevention of mother-to-child transmission, but will be unaffordable to continue after delivery for almost all medical schemes. Nelfinavir has also been shown to be effective and safe for paediatric use, and will be used in this setting as requested and if affordable.

In a recent randomized trial comparing nelfinavir to lopinavir/ritonavir (Kaletra®), nelfinavir was associated with a higher failure rate (NEJM 2002;346:2039). In the trial there were similar proportions of patients who had to discontinue medication due to side effects. The side effect profile of nelfinavir is similar to that of the other PIs - GIT intolerance (mainly diarrhoea) and hyperlipidaemias. The risk of hyperlipidaemias is relatively low.

Nelfinavir was originally used 8 hourly. However, as with any medication, the middle dose is often skipped. It is possible to administer nelfinavir twice daily, but this requires a slightly higher total daily dose with a high pill burden, which is known to reduce adherence. Furthermore, the higher dose means that pharmacies have to split packs. This results in a relatively high price (see table). Nelfinavir can therefore only be authorized for limited indications.

	Dose	Tabs/Day	Price/Month*
Vira-cept®	1250mg bd	10	R913.78
Kaletra®	400/100mg bd	6	R527.40
Crixivan®+Norvir®	800/100mg bd	6	R486.04

*Cost price incl. VAT + R50 professional fee per ARV per month.

In summary nelfinavir is still expensive and has a high pill burden. It is less potent than Kaletra®. AfA will authorize nelfinavir together with two NRTIs during pregnancy (preferably starting in the 2nd trimester) for women who cannot use nevirapine (either due to intolerance or failure). Long term use of nelfinavir will be reserved for patients unable to tolerate other PIs - this will need to be discussed with AfA.

Guidelines for Managing Lipid Disorders

Fasting lipids (including triglycerides, LDL and HDL cholesterol) should be done at baseline in all patients starting protease inhibitors. This should be repeated in 3-6 months and then annually thereafter. Lifestyle modification should be advised for all elevations (stop smoking, lose weight if relevant, increase exercise, reduce cholesterol and saturated fat intake).

Levels which may require additional therapy:
Triglycerides >5.6mmol (after diet)
LDL >4.9mmol (>3.4mmol if 2 or more IHD risk factors)

Fibrates should be used for elevation in triglycerides.
Atorvastatin (5-10mg starting dose) or pravastatin (20mg starting dose) for LDL cholesterol or for mixed LDL cholesterol and triglyceride elevations. The goal of statin therapy should be to lower LDL cholesterol <4.1 mmol (or <3.4 mmol if 2 or more risk factors are present). AVOID combining statins and fibrates in general as the drug interactions make the serious complication of rhabdomyolysis more likely.

Reference:
Schambelan M, Benson CA, Carr A et al. Management of metabolic complications associated with antiretroviral therapy for HIV-1 infection: recommendations of an International AIDS Society-USA panel. JAIDS 2002;31:257-275

Drug interaction OF THE MONTH

Antiretrovirals and Anaesthetics:

Because many of the agents utilised in anaesthetics interact with antiretroviral agents, it is important to consider this aspect of a patient's medical history when referring a patient for surgery, or when administering any form of anaesthetic or pre-medication. In general terms, interactions occur due to synergistic side effect profiles (e.g. nevirapine and hepatotoxic anaesthetic agents) and / or due to drug - drug interactions reducing or increasing active metabolites with potentially dangerous effect. A general rule of thumb is that liver metabolised drug levels may be affected by the protease inhibitors and the NNRTI class. Protease inhibitors (particularly ritonavir) inhibit cytochrome P450, increasing blood levels of agents metabolised by this enzyme system. Thus, drugs such as midazolam and diazepam co-administered with protease inhibitors may have prolonged and elevated blood levels. This may result in unexpectedly prolonged sedation and respiratory depression. NNRTIs (nevirapine and efavirenz) are cytochrome P450 inducers, resulting in decreased levels of drugs co-metabolised by this enzyme system, such as warfarin.

Changing from dual NRTI Therapy to HAART

Our records indicate that about 11% of AfA patients on antiretroviral therapy are still receiving only dual NRTIs. Many were started prior to the recent substantial price reductions and could now, depending on their medical scheme option, access HAART, which has a far more durable response.

Doctors are requested to review the therapy of patients still on dual therapy and to discuss changing to HAART with their patients.

A recent viral load should be obtained. Patients who are undetectable (< 50 copies) could, in the view of some experts, stay on their dual therapy. Those with a detectable viral load should change to a new NRTI combination plus a NNRTI (neviripine or efavirenz) or a boosted PI. If all the NRTI combinations have failed, the combination of a NNRTI plus a boosted protease inhibitor can be considered.

Treatment intensification (i.e. simply adding a third agent) carries the very real risk of viral resistance and should only be attempted if the dual NRTI therapy has just been started (< 6 months) and does not include 3TC®. Patients with low level viraemia (viral loads between 50 and 400) could also be considered for intensification. A boosted protease inhibitor rather than a NNRTI should be used as there is less risk of resistance developing. A third agent should never be added to a failing regimen.

Please refer to the Clinical Guidelines or contact our clinical staff on 0800 227 700 for more information and assistance with specific patients. AfA can also be contacted for information about the availability of funds for different medical scheme options.

Practice point OF THE MONTH

Managing ART Related Diarrhoea

Many of the antiretroviral agents are associated with gastrointestinal side effects, notably nausea, vomiting and diarrhoea. These occur primarily with the NRTI and protease inhibitor classes. While diarrhoea may be caused by many agents and combinations of agents, it is most commonly associated with the use of didanosine (ddI, Videx®), and the protease inhibitor nelfinavir (Vira-cept®). Management includes the exclusion of other aetiologies (e.g. viral and bacterial enteropathies) and the assessment of the severity of the diarrhoea. If judged to be associated with the antiretroviral regimen, treatment includes adequate hydration, the use of antimotility agents such as loperamide and codeine phosphate, bulking agents such as isusphagula husk (Fybogel®), and, in the case of nelfinavir induced diarrhoea, adjunctive use of calcium carbonate or gluconante (600mg bid po). If severe and non responsive to these measures, the regimen may need to be adjusted, or stopped.

Structured Treatment Interruptions

The immune system fails to eradicate or even adequately control HIV replication. During successful HAART, suppression of HIV replication occurs - this is defined as an undetectable viral load. It has been shown that cellular immunity to HIV declines in patients who achieve an undetectable viral load. It was hoped that short cycles of stopping HAART so called structured treatment interruptions - in patients who achieve an undetectable viral load would allow the immune system to respond to HIV antigens as the viral load rebounds. Patients could then discontinue therapy and maintain a lower viral load or even an undetectable viral load. Initial studies in seroconversion illness (primary HIV infection) supported this hypothesis[1], although no randomized placebo-controlled studies have been done in this setting. Further advantages of structured treatment interruptions include reduced cost (very attractive in South Africa!) and reduced toxicity.

Reports of structured treatment interruptions in patients with established HIV (i.e. beyond seroconversion) have given very disappointing results[2]. Improved immunity has not been shown. Furthermore, there is a high rate of development of resistance during treatment interruptions. There is also a risk of developing the features of primary HIV infection during viral rebound. Thus there is currently no role for structured treatment interruptions in established HIV infection.

Two recent reports do suggest a potential role of a single treatment interruption prior to commencing salvage therapy[3,4]. In this setting patients with multi-drug resistance interrupt therapy for a few months (median 20 weeks in one study[3] and 8 weeks in the other[4]). During the interruption the resistant HIV populations decline in number as the drug-sensitive "wild" virus is more fit and replicates faster. Starting the same therapy again would confer no long-term benefit as resistance persists even if the resistant populations decline below the level that they can be detected. However, provided that at least one new drug is used to which the patient's HIV is sensitive, a durable response can occur[3]. Disease progression during a treatment interruption in this setting is a real risk, as illustrated by the development of significant HIV-related complications in 3/24 patients in one study[3].

In summary, structured treatment interruptions appear to have a role in primary HIV infection (seroconversion illness) - AfA will approve HAART for a limited period in this setting. These patients must be monitored very closely. There is currently no role for structured treatment interruptions in patients with established HIV. A single treatment interruption may have a role prior to commencing salvage therapy.

References

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3. Deeks SG, Grant RM, Wrin T, Paxinos EE, Liegler T, Hoh R, Martin JN, Petropoulos CJ. Persistence of drug-resistant HIV-1 after a structured treatment interruption and its impact on treatment response. AIDS 2003 Feb 14;17(3):361-70.

4. Katlama C, Dominguez S, Duvivier C, et al. Long-term benefit of treatment interruption in salvage therapy (GIGHAART ANRS 097). 10th Conference on Retroviruses & Opportunistic Infections, Feb 2003 Boston. Abstract #68.