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Nevirapine and Pregnancy - New Concerns

Single dose nevirapine (to the mother in labour and to the infant) is effective and safe in preventing mother to child transmission (MTCT). As a result this simple intervention has been implemented in many resource-constrained settings, including the South African public sector. It is known that HAART is the most effective way to prevent MTCT and nevirapine is often recommended as a component of a HAART regimen in pregnancy. New information has become available that is a cause of concern for both single dose nevirapine and using nevirapine as part of HAART.

The main concern about single dose nevirapine is the emergence of resistance. Studies have shown that resistance develops after single dose therapy in 20 to 60% of women. This resistance is high level and nearly always also confers cross-resistance to the other non-nucleoside reverse transcriptase inhibitor (NNRTI), efavirenz. Following single dose use, nevirapine is detectable in the blood for 2 to 3 weeks. This gradually falling level is the ideal environment to select out HIV mutants that have NNRTI mutations. On follow up the resistant population of HIV mutants declines in the absence of the selection pressure of ongoing exposure to nevirapine and, after a few months, resistance is no longer detectable. However, it is known from studies of resistance developing on long term antiretroviral therapy that these resistant mutants, even though no longer detectable, are archived and rapidly re-emerge upon re-exposure to the antiretroviral. But there was no evidence that this occurred after single dose use until a recent congress report of a Thai study. This showed that women who commenced HAART (consisting of nevirapine and two nucleoside reverse transcriptase inhibitors) within 6 months of delivery were much more likely to fail virologically if they had developed NNRTI resistance following single dose nevirapine compared with women who received zidovudine for MTCT. Alarmingly, women who had received single dose nevirapine without developing detectable resistance also had a poorer outcome, although their failure rates were much lower than women who had detectable resistance. It remains to be seen whether HAART containing an NNRTI commenced more than 6 months following single dose nevirapine will also experience high failure rates. Until this is known it is prudent to avoid single dose nevirapine for MTCT in settings where alternative approaches are available.

The second concern relates to the use of nevirapine as a component of a HAART regimen in pregnancy. Nevirapine-induced hepatotoxicity is a well known adverse event and regular monitoring of ALT is recommended, especially in the first 8 weeks. It is known that women are at higher risk than men of developing hepatotoxicity. It has also become clear that patients with higher CD4 counts are at increased risk of developing hepatotoxicity. Women with CD4 counts >250 cells/mm^3 experience significant hepatitis (defined as ALT elevations of more than fivefold above the upper limit of normal) at rates of around 20%. Anecdotal reports suggest that in pregnancy this risk may be even higher. Thus caution is advised when using nevirapine as a component of HAART in pregnant women with high CD4 counts. More frequent ALT monitoring should be carried out or an alternative agent selected.

Practice point OF THE MONTH

The Role of Abacavir (Ziagen®)

1 Abacavir (ABC) is a guanine analogue Nucleoside analogue Reverse Transcriptase Inhibitor (NRTI). It is more potent than other agents in its class, causing a 1.5-2.0 log drop in viral load in treatment naïve patients. Early studies of ABC combined with AZT and 3TC showed promising results in patients with low viral loads, but subsequent clinical trials showed high failure rates with this triple NRTI regimen, and it is no longer recommended.

2 Resistance to ABC is conveyed by the acquisition of 3 thymidine analogue mutations (AZT and d4T) and the M184V mutation generated by 3TC exposure. Thus it is not usually effective in salvage regimens.

3 ABC is easy to use, with a favourable side effect profile. Approximately 5% of patients, however, will develop a hypersensitivity reaction (high fever, myalgia, rash, upper respiratory tract symptoms, GIT symptoms), generally within the first 6 weeks of therapy. Should this occur, the drug should be immediately discontinued. Fatal reactions have occurred in patients rechallenged after hypersensitivity reactions, and this should never be attempted.

4 ABC remains very expensive, which precludes its widespread use.

For the above reasons, AfA is adopting the following policy regarding abacavir:

- The use of ABC should only be undertaken after discussion with the AfA clinical committee.
- Abacavir is considered a specialist drug, and should only be used by or under supervision of an expert treater.

Immune "boosters" in HIV infection

Immune modulation with phytosterols (Moducare®)
A mixture of the plant sterols (phytosterols) beta-sitosterol and its glycoside, Moducare®, is widely promoted as an "immune booster" in HIV infection. Studies of Moducare® have been conducted by researchers at the University of Stellenbosch.

They have shown several effects on immunity in vitro:

1. Lymphocyte proliferation in response to mitogenic stimulation is enhanced.
2. Increased lytic ability of natural killer cells.
3. Increased Th1 immune response and unchanged or inhibited Th2 response.
4. Inhibition of the pro-inflammatory cytokines, Interleukin 6 and TNF-α.

Thus Moducare® has effects on the immune system that are both stimulatory and inhibitory - it is thus more accurate to call it an immune modulator rather than an immune booster.

The net effect of these various immune effects in individuals who are HIV-infected is difficult to predict. The enhanced Th1 immune responses might be beneficial as the Th1 response is important in responding to intracellular pathogens that are important in HIV (including the virus itself). The inhibition of the pro-inflammatory cytokines would reduce immune activation, which is thought to be important in accelerating HIV disease progression. However, the immune stimulatory effects (e.g. on lymphocyte proliferation) might be harmful as this would enhance immune activation and lead to increased HIV replication.

Animal studies on a feline model of feline immunodeficiency virus have shown that the CD4 lymphocyte count remains higher in the Moducare® treated cats. However, the numbers of cats studied is small, it is unclear whether any blinding was carried out and the study has never been published in a peer-reviewed journal.

A human study in HIV-infected adults was also conducted. There were no placebo controls. The researchers claim that CD4 lymphocyte counts remain stable in treated patients. However, anecdotally several of their research subjects were on antiretroviral therapy - it is unclear whether they were aware of this. Once again the study has never been published in a peer-reviewed journal. The researchers claim "reduced viral load" without specifying how much. They state that Moducare® has no antiviral effect and ascribe the reduction in viral load to reduced immune activation.

A small controlled trial was carried out in adults with tuberculosis. There was no improvement in sputum conversion rates, but the subjects treated with Moducare® had improved weight gain. There were differences noted in the differential white cell count, notably with a rise in eosinophil count that could point to hypersensitivity.

In summary, there are grounds for believing that Moducare® might be beneficial in HIV, but equally there is concern that it could be harmful. The only way to discover whether Moducare® has any role in HIV infection would be to conduct a randomized controlled trial. This would need to be done by a different group as all the research has come from one source.

African potato
The African potato or hypoxis plant is widely used by traditional healers. It is a rich source of phytosterols. However it has been found to be a toxic agent with bone marrow toxicity and severe hepatotoxicity. Thus this agent should be avoided.

Sutherlandia frutescens
This traditional herbal remedy is widely used in South Africa. Animal studies conducted by the Medical Research Council failed to show any significant toxicity. No published studies exist on human toxicity or use for any indication.

Micronutrients
It is well known that malnutrition impairs many physiological functions, including the immune response. Micronutrients that have a particular role in immunity include zinc and vitamin A. Malnutrition is common in advanced HIV disease due to wasting from many causes including anorexia from depression or HIV, diarrhoea, catabolic state induced by either opportunistic diseases or HIV itself. Thus it is logical that malnutrition should be avoided where possible in HIV infection or treated appropriately when it occurs. Oxidative stress is increased in HIV infection. Many micronutrients have anti-oxidant properties, including ß-carotene, vitamin C, vitamin E and selenium. Both oxidative stress and immune dysfunction are thought to be important co-factors in HIV infection.

There are a large number of studies - including several in Southern Africa, that show low levels of micronutrients in HIV infection, especially in more advanced disease. Many small studies show improvement in CD4 lymphocyte counts and several other immune functions in subjects given micronutrients. Several large randomized controlled trails in HIV-infected pregnant women (including South African studies) show several maternal and child benefits, but the effects on HIV transmission were contradictory. Trials in HIV-infected children show benefit. A trial in Zambian adults with diarrhoea and wasting failed to show benefit.

Because of the above evidence and because micronutrients are safe (unless given in high doses), it is generally recommended that micronutrient supplementation should be given to HIV infected individuals - especially pregnant women and children. Excessive doses of micronutrients is harmful - particularly the fat soluble vitamins. There are also studies in HIV infection showing that high supplemental doses of zinc are harmful.

Summary
Of the available "immune boosters" there is insufficient evidence to recommend Moducare®. There is good evidence that African potato is harmful. Micronutrient supplementation, provided the doses are not too high, clearly benefits HIV-infected pregnant women and children. The benefits of micronutrient supplementation in other HIV settings is unclear, but there is suggestive evidence that it may be beneficial and good evidence that it is not harmful.

Drug interaction OF THE MONTH

Protease Inhibitors and Benzodiazepines

Protease inhibitors (particularly ritonavir) inhibit Cytochrome P450, increasing blood levels of agents metabolized by this enzyme system. Thus, drugs such as the benzodiazepines co-administered with protease inhibitors may have prolonged and elevated blood levels. This may result in unexpectedly **prolonged sedation** and **respiratory depression**.

Increase in 0199 Payment

The payment of the 0199 account for the completion of an Aid for AIDS Application form has been R150. According to the NRPL (National Reference Pricing List) the recommendation is to increase this fee to R169.90.

This increase has been accepted by all medical schemes and will be implemented, for all new Aid for AIDS applications, from 1 March 2004.

Please note that the 0199 payment is only made to doctors who register South African medical scheme members / dependants on AfA.

Scheme Changes for 2004

The following changes took place on 1 January 2004.

New schemes contracted to Aid for AIDS:

- Netcare
  - Savings option - AfA benefit of R25 000 per beneficiary per annum.
  - Medi-Cross option - AfA benefit of R25 000 per beneficiary per annum.

New corporates contracted to Aid for AIDS:

- Afrox Industrial (contracted to AfA on 1 Feb 2004)
- Nestle (contracted to AfA during March 2004)
- Roche (will be contracting to AfA on 1 May 2004)

The AfA programme is available to employees of these companies. Employees may only be registered by contracted doctors. In some cases the medical scheme HIV benefit (if available) must be exhausted, before the AfA benefit is available.

New scheme options contracted to Aid for AIDS:

- Fedhealth Ultima Access option. Aid for AIDS benefits of R5 300 per member family per annum for MTCT* prophylaxis or PEP* only.
- Liberty Platinum Xtreme. Aid for AIDS benefits of R25 000 per beneficiary per annum. R8 250 for post rape and R7 100 for needlestick and MTCT* prophylaxis.
- Liberty Gold Advantage. Aid for AIDS benefits of R20 000 per beneficiary per annum. R7 000 for post rape and R5 900 for needlestick and MTCT* prophylaxis.

Scheme options which have been discontinued:

- Liberty Gold Complete option
- Liberty Gold Cap option
- Meridian Traditional Unlimited option

Scheme options leaving Aid for AIDS:

- Aacmed Standard Care option (The Managed Care option is still contracted to AfA.)
- Nimas Quantum option (The Premium and Optimum options are still contracted to AfA.)

Please note: AfA do have a complete list of all contracted schemes and the AfA limit. Please contact 0860 100 646 if you would like a copy or visit our website - www.aidforaids.co.za.

Benefit Changes:

Scheme	Option	Change
Aacmed	Managed Care	AfA benefit increased to R32 400 per beneficiary per year.
AECI	Basic Carecross	MTCT* prophylaxis is paid from the overall annual limit, not the AfA limit.
Bonitas	Boncap and Primary	These options previously only covered MTCT* prophylaxis and PEP*. They now also cover ongoing ART. The benefit remains R7 500 per beneficiary per annum.
Fed-health	Ultima 200	AfA benefit increased to R18 000 per member family per annum.
Fed-health	Ultima 300	AfA benefit increased to R20 000 per member family per annum.
Fed-health	Ultima Core	AfA benefit increased to R5 300 per member family per annum for MTCT* prophylaxis or PEP* only.
Fed-health	Maxima Plus	AfA benefit increased to R20 000 per member family per annum.
Fed-health	Maxima Standard	AfA benefit increased to R18 000 per member family per annum.
Fed-health	Maxima Core	AfA benefit increased to R5 300 per member family per annum for MTCT* prophylaxis or PEP* only.
Fed-health	Ultimax	AfA benefit increased to R20 000 per member family per annum.
Liberty	Platinum Focus	AfA benefit increased to R25 000 per beneficiary per annum, R8 250 for post rape and R7 100 for needlestick and MTCT* prophylaxis.
Liberty	Platinum Complete	AfA benefit increased to R25 000 per beneficiary per annum, R8 250 for post rape and R7 100 for needlestick and MTCT* prophylaxis.
Liberty	Silver	AfA benefit increased to R15 000 per beneficiary per annum, R2 200 for post rape and R2 640 for needlestick and MTCT* prophylaxis.
Liberty	Gold Focus	AfA benefit increased to R17 500 per beneficiary per annum, R6 600 for post rape and R5 500 for needlestick and MTCT* prophylaxis.
Nampak	Nampak	AfA benefit increased to R21 400 per beneficiary per annum.
Omni-Health	All options	The AfA limit is now subject to the Overall Annual Limit
SABC	SABC	No levy for AfA scripts anymore.
Topmed	80%, 100%, Exec and Incentive	AfA benefit increased to R1 333 per beneficiary per month.
Wits	Wits	AfA benefit increased to R48 000 per beneficiary per annum.

**MTCT = mother-to-child transmission*

** PEP = post-exposure prophylaxis*

Aid for AIDS has moved!

Our new contact details are as follows:

Reception: +27 (0)21 514 1700

Doctors & pharmacists: +27 (0)21 514 1768 or 0800 22 77 00

Patients: +27 (0)21 514 1769 or 0860 100 646

Fax: +27 (0)21 514 1771 or 0800 600 773

Physical address: The Park, Park Road, Pinelands, Cape Town, 7405
Postal address: P O Box 38597, Howard Place, Pinelands, 7450

Kaletra® and Rifampicin

Co-administration of rifampicin with Kaletra® 400mg/100mg twice daily results in a decrease in Kaletra® to subtherapeutic levels. This may lead to a loss of virological response and possible resistance.

A study has shown that giving lopinavir/ritonavir at a dose of 400mg/400mg bd with rifampicin produced comparable pharmacokinetic results relative to lopinavir/ritonavir 400mg/100mg bd without rifampicin.

Using an increased dose of ritonavir (Kaletra® 3 capsules bd with Norvir® 3 capsules bd) allows concurrent use of rifampicin and Kaletra®.

Reference
Pharmacokinetics of two adjusted dose regimens of lopinavir/ritonavir in combination with rifampicin in healthy volunteers. La Porte CJL, Colbers EPH, Bertz R, et al. 42nd Interscience Conference on Antimicrobial Agents and Chemotherapy, San Diego, September 2002, Poster A-1823.

HAART and Porphyria

There is very limited information on the safety of antiretrovirals in patients with acute porphyria. It is likely that nucleoside reverse transcriptase inhibitors (e.g. zidovudine) will be safe. The protease inhibitors are thought to be unsafe, with one report of an attack induced by indinavir. There is no data on non-nucleoside reverse transcriptase inhibitors. Close monitoring of patients with acute porphyria needing HAART is advised - contact the porphyria service at the University of Cape Town for advice: +27 (0)21 406 6332.