Nevirapine toxicity — implications for management of South African patients

Robin Wood

Public debate and new nevirapine toxicity data

Nevirapine was the first non-nucleoside drug (NNRTI) to be approved by the Federal Drug Administration (FDA) for use in combination therapy of HIV-1 infection in 1996. It has been approved for use in children of 2 months or older, and following the publication of the HIVNET 012 study in Uganda has been widely used as single-dose prophylaxis for prevention of mother-to-child HIV transmission (MTCT) in resource-poor settings.

Early in nevirapine development, a cutaneous hypersensitivity rash occurring in the first 4 weeks of therapy was recognised as a common side-effect, and registration studies reported clinical hepatitis in approximately 1% of individuals. Despite these recognised toxicities, cheap generic formulations, including fixed-dose combinations, have been manufactured in India and Brazil, making nevirapine one of the most commonly prescribed antiretrovirals worldwide.

Clinical experience with the drug has been extensive; however, it has recently attracted increased media scrutiny, becoming embroiled in controversy. Firstly an ongoing dispute between Dr Jonathan Fishbein and his employers at the National Institutes of Health (NIH) over the conduct of HIVNET 012 was given wide media coverage when Associated Press released articles accusing the NIH of conspiring to suppress data about the safety of short-course nevirapine given to African patients. Parallels were drawn with the infamous Tuskegee study. The initial Associated Press report appeared on 13 December 2004, provoking a series of polarised responses over the next few days from the Elizabeth Glaser Paediatric AIDS Foundation, Project Inform, The National Institutes of Health and the South African National Congress, and a rebuttal from the researchers at Makerere and Johns Hopkins universities. Concerns were expressed in leading scientific journals (including Science, Nature and the BMJ) that these allegations might undermine MTCT programmes. Nevirapine-related toxicities in pregnancy were highlighted by a study published in 2004, reporting a death from fulminant hepatitis in a Paediatric AIDS Clinical Trials Group study (PACTG 1022). Reports that intrapartum exposure to nevirapine was associated with increased virological failure during subsequent nevirapine treatment increased concerns.

Finally, the US Federal Drug Administration issued a Public Advisory for Nevirapine (Viramune), informing health care providers of a safety-related change to the nevirapine package insert. This advisory was based on data showing a higher risk of serious liver toxicity in patients with preserved CD4 cell counts commencing nevirapine.

This article will review these new data and discuss resulting changes in patient management in South Africa, both within the national roll-out programme and other health sectors.

Nevirapine toxicity and the FDA Public Health Advisory

The FDA Public Health Advisory for Nevirapine issued on 19 January 2005 notified a change in nevirapine prescribing information with a warning against starting nevirapine in women with a CD4 cell count > 250 µl and in men with a count > 400 µl. The risk of developing a hepatic hypersensitivity reaction in the first 6 weeks of nevirapine therapy had been shown to be increased 12-fold in women with CD4 counts > 250 and 5-fold in men with counts > 400 compared with women with counts of < 250 and men with counts of < 400, respectively.

The recent reporting of such serious toxicity after 9 years of nevirapine registration and widespread use highlights the need for ongoing monitoring of nevirapine toxicity.

Clinical presentation

<table>
<thead>
<tr>
<th>Clinical presentation</th>
<th>Associated risk factors</th>
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<tr>
<td>Early symptomatic + rash</td>
<td>Female gender</td>
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<tr>
<td>Early asymptomatic &lt; 42 days</td>
<td>High CD4 counts</td>
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<tr>
<td>Late symptomatic &gt; 42 days</td>
<td>HLA-DRB1*0101</td>
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<tr>
<td>Asymptomatic</td>
<td>Most antiretrovirals</td>
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<td></td>
<td>Hepatitis B and C</td>
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<td></td>
<td>infection</td>
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<tr>
<td></td>
<td>Mitochondrial toxicity</td>
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<td></td>
<td>Immune restoration</td>
</tr>
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<td></td>
<td>Alcohol etc.</td>
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Fig. 1. Percentage of patients with hepatotoxicity (AST/ALT > 5 × ULN), clinical presentations and associated risk factors identified in a meta-analysis of 17 studies including 2 545 nevirapine-treated subjects. Hepatotoxicity occurred in 10%, and was associated with rash and/or systemic symptoms in 3.9% of subjects and with rash in 2.2%.
difficulties of quantifying rare adverse events. The problem was made more complicated because hepatic abnormalities are common in HIV infection due to coinfections with hepatitis B and C, alcoholism, substance abuse and co-administration of other medications including antiretrovirals associated with hepatotoxicity. Also data accumulated from different sources appeared to give conflicting results. Large cohort studies such as the EuroSIDA study of 4 639 patients initiating therapy with an NNRTI reported reassuringly low rates of ALT/AST elevations (> 5 × upper level of normal (ULN)) of 1.7% for efavirenz and 2.1% for nevirapine, and liver failure rates of 0.4 and 0.3 cases per 100 person-years, respectively.18 However, toxicity databases raised concern by reporting serious hepatotoxicities and deaths, while controlled trials gave widely differing estimates of nevirapine hepatic risk.19,20

A fuller picture has only developed with the recognition that there is a spectrum of drug-related hepatic toxicity in treated HIV infection. Low elevations of AST/ALT (< 5 × ULN) occur frequently in patients on antiretroviral therapy during the course of treatment, are nonspecific and have multiple causations. Moderate elevations (> 5 × ULN) occur in 6% of treated patients, and are associated with co-infection with hepatitis C (relative risk (RR) = 5.2), elevation of baseline AST/ALT (RR = 4.3) and hepatitis B co-infection (RR = 2.3) and weakly associated with nevirapine.21 Hypersensitivity hepatitis (defined as AST/ALT > 5 × ULN with systemic symptoms and/or rash occurring in the first 42 days of antiretroviral therapy) is a specific entity strongly associated with nevirapine use (RR = 11.2) and is modified by gender and CD4 count (Fig. 1).22

The low reported incidence rate of nevirapine hypersensitivity hepatitis (cases/100 person-years) in cohort studies may in part be due to a few events occurring early in treatment divided by a very large time denominator of total cohort follow-up. A genetic predisposition to hypersensitivity reactions has recently been recognised to be associated with a human leucocyte antigen marker (HLA-DRB1*0101).23 Some of the variability in reported toxicity between populations may also be related to a differential HLA-DRB1 carriage frequency, which is high in USA and European Caucasian populations, but lower in African and Asian populations.24

Single-dose nevirapine for prevention of MTCT of HIV and HIVNET 012

The Associated Press articles of 13-15 December raised concerns that there may be many unreported adverse events related to nevirapine use. The investigators at Makerere University and Johns Hopkins denied suppressing drug-related toxicities in the safety reporting and stated that no deaths or serious adverse events definitely related to nevirapine occurred during the study.

While the debate around HIVNET 012 has implications for design and conduct of studies in resource-poor settings, it does not give any direct evidence of toxicity of single-dose nevirapine in pregnant women. Several large studies and data sets have subsequently established the safety of single-dose nevirapine alone and in combination with other antiretrovirals in a wide variety of settings. No significant clinical or laboratory toxicities were observed in 1 600 women receiving single-dose nevirapine in comparative clinical trials.25 A South African study involving 1 317 pregnant women, of whom 655 received single-dose nevirapine and 662 received zidovudine with lamivudine, reported in 2003 no significant laboratory or clinical toxicities in the mothers. The rate of hepatic events in the infants was 3.3% in the ZDV/3TC and 2.7% in the NVP arms.26 In a study of 1 270 non-breast-feeding women recruited in the US, Europe, Brazil and the Bahamas to receive single-dose nevirapine or placebo in combination with standard ART, the HIV transmission rate was 1.5% and there were no significant safety concerns. Elevated transaminases, defined as > 2.5 × ULN, occurred in 1% of subjects.27

Between January 2001 and February 2003, 1 445 Thai women receiving zidovudine in the third trimester of pregnancy were given additional single-dose nevirapine, with no reported grade 3 or 4 hepatotoxicity. Of the 216 serious adverse events that occurred during the study, 59% were pregnancy-related and 26% HIV-related; 7% of women developed anaemia possibly related to zidovudine, and there was a single case of allergic reaction which may have been related to nevirapine.28 Up to 2004, no serious nevirapine-related liver toxicity had been reported to the USA FDA Medwatch programme for women receiving single-dose nevirapine.29 This combined weight of evidence indicates that single-dose nevirapine alone and in combination with other ARTs is free of significant hepatic toxicity and can be prescribed safely in pregnancy. Single-dose nevirapine is less effective than more complex regimens, however, and there is increasing evidence that virological suppression to < 50 copies/ml is lower in women who have received single-dose nevirapine subsequently treated with NNRTIs.30 The cheapness and ease of administration however continue to makes it an attractive MTCT prevention strategy in settings where more complex regimens are not available.

Use of continuous nevirapine in pregnancy and PACTG 1022

The use of antiretrovirals in pregnancy impacts on both maternal and fetal health. Nevirapine is an FDA category C drug, indicating no teratogenicity in animal studies but a lack of well-controlled trials in pregnant women. The antiretroviral pregnancy registry, however, has not shown to date that nevirapine use is associated with increased birth defects.31

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Nevirapine-containing regimens have been widely used in MTCT programmes and together with other interventions have brought transmission rates to < 1%. Women in industrialised societies frequently start ART for the first time during pregnancy, the majority having CD4 cell counts of > 250 cells/µl.

The risk of nevirapine to maternal health was highlighted in June 2004 by the publication of the PACTG 1022 comparative study of neflavinavir and nevirapine in pregnancy. The study received prominence because a woman with a baseline CD4 count of 330/µl developed > 5 x ULN AST at 4 weeks, continued receiving nevirapine for a further 6 days and subsequently died of hepatic necrosis. The study was small and although 17.6% of women in the nevirapine arm developed AST/ALT > 5 x ULN, the confidence intervals for this estimate are very wide (95% CI –0.5 to +36), encompassing rates reported in all other studies. The continuation of nevirapine in the presence of an elevated AST may also have contributed to the maternal death. The authors raised the question of whether pregnancy could be an independent risk factor for nevirapine toxicity. Six deaths from hepatic failure occurring during pregnancy and the puerperium have been reported to the FDA Adverse Event Reporting System. Three deaths were from hepatic necrosis associated with NVP and 3 from lactic acidosis associated with ddI/ddT-containing regimens. However owing to lack of a denominator it is difficult to use these data to establish pregnancy as an independent risk factor for hepatitis. Retrospective chart reviews of women receiving nevirapine have not shown increased hepatotoxicity compared with non-pregnant populations. Pregnancy may therefore not be a specific risk factor; however, nevirapine hypersensitivity reactions are more frequent in women with CD4 counts above 250 cells/µl and this is a profile that frequently matches pregnant women receiving MTCT prophylaxis.

**Nevirapine use in post-exposure prophylaxis**

Nevirapine has characteristics that make it potentially attractive for post HIV-exposure prophylaxis (PEP), including rapid antiviral activity of the parent molecule, which does not require intracellular phosphorylation, and a low pill burden. In September 2000, two cases of life-threatening hepatotoxicity, including one requiring liver transplantation, were reported in health workers receiving continuous nevirapine for PEP. Up to September 2000 the FDA MedWatch adverse event monitoring programme had received 22 reports of serious adverse events, 12 of which were hepatic and 14 cutaneous, in individuals receiving nevirapine-containing PEP regimens. In March 2001 a letter in The Lancet reported a high frequency of serious adverse events among a series of 57 individuals receiving nevirapine PEP. The use of nevirapine for PEP was recently re-explored in a report of 120 individuals treated with 200 mg nevirapine for 4 days together with 2 nucleoside reverse transcriptase inhibitors for 28 days at the University Hospital of Strasbourg. Nevirapine was well tolerated in this regimen, but minor elevations in ALT were reported in 6 individuals (5.6%). Current PEP guidelines from the US, Europe and the UK specifically discourage use of nevirapine for PEP.

**Implications of new nevirapine data for antiretroviral programmes in South Africa**

Risk analyses on which the FDA advisory was based, derived data from clinical trial data. Although a genetic predisposition has been postulated and race was associated with hepatitis risk in some individual studies, it did not remain as a significant association in the overall meta-analysis. Whereas the FDA advisory on changing prescribing information has little impact in developing countries where there is easy availability of alternative ARVs, in resource-poor settings alternatives are limited by both cost and availability. Therefore the risk-benefit analysis may be very different from that in industrialised settings.

**Single-dose nevirapine for MTCT**

While single-dose nevirapine for MTCT is not optimal as far as efficacy is concerned and may negatively impact on subsequent maternal virological response to ART, it has been demonstrated to be safe from serious hepatic toxicity.

**Post-exposure prophylaxis (PEP)**

Use of nevirapine for PEP has been associated with unacceptable toxicity and as safer alternatives are available there is no role for nevirapine in PEP regimens in South Africa.

**Initiating and switching combination therapies**

Present World Health Organization and South African guidelines recommend initiation of ART with NNRTIs. Efavirenz is the only alternative NNRTI available in South Africa. It has a similar efficacy to nevirapine but a different toxicity profile and is a possible teratogen, and should be avoided in women of child-bearing potential (WOCBP). Nevirapine therefore continues to fill an important role in combination therapy until cheap and safe alternatives are available. Most current ART guidelines do not recommend initiating therapy for males with CD4 counts > 400 cells/µl and those with lower CD4 cell counts can safely initiate ART with either NVP or EFV, the choice being determined by toxicity profile and/or cost.

In contrast, WOCBP with high CD4 cell counts frequently initiate combination therapy in industrialised societies during April 2005, Vol. 95, No. 4 SAMJ
pregnancy and an increasing number of South African women with CD4 cell counts that have risen above 250/µl wish to switch from EFV before falling pregnant. Women who initiate or switched to nevirapine at a CD4 cell count >250/µl are now recognised to be at high risk of hypersensitivity reaction and will require alternative management strategies as outlined in Table I.

Conclusion

Hepatic toxicity occurs in approximately 6% of patients taking ART and is due to multiple causes with various risk factors. Nine years after registration of nevirapine, early hypersensitivity reactions, occurring in approximately 2% of patients, have been recognised to be a distinct clinical entity strongly associated with nevirapine use, female gender and a high CD4 cell count. This new insight resulted from a more precise syndrome definition and a meta-analysis of clinical trials. Long-term use of nevirapine has a similar adverse event rate as alternative therapies and therefore continues to have a major role in HIV patient management. Laboratory monitoring of liver function tests and increased clinical vigilance is required to identify hypersensitivity reactions, consisting of elevated hepatic enzymes with rash and/or other clinical symptoms such as fever, nausea and abdominal pain, occurring in the initial 6 weeks of nevirapine therapy. Liver function tests should be performed when a nevirapine rash is present. Once a diagnosis of nevirapine hypersensitivity reaction is made, or strongly suspected, nevirapine must be discontinued as soon as possible and not rechallenged.

Table I. Present policies for initiating antiretroviral treatment in women and possible strategies accommodating change in nevirapine prescribing information

<table>
<thead>
<tr>
<th>Females CD4 &lt; 250</th>
<th>Present policy</th>
<th>Possible strategy</th>
<th>Problems/advantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not WOCBP**</td>
<td>NVP or EFV</td>
<td>No change</td>
<td>Monitor for hepatotoxicity</td>
</tr>
<tr>
<td>WOCBP*</td>
<td>NVP</td>
<td>Encourage initial use of NVP</td>
<td>Avoids switch to NVP when CD4 counts recover</td>
</tr>
<tr>
<td>Pregnant</td>
<td>NVP</td>
<td>No change</td>
<td>Monitor for hepatotoxicity</td>
</tr>
<tr>
<td>Females CD4 &gt; 250</td>
<td>NVP or EFV</td>
<td>Initiate EFV</td>
<td>Higher cost than NVP</td>
</tr>
<tr>
<td>Not WOCBP**</td>
<td>NVP or EFV</td>
<td>Initiate EFV</td>
<td>May require switch to other drug if future pregnancy planned</td>
</tr>
<tr>
<td>WOCBP* taking contraception*</td>
<td>NVP or EFV</td>
<td>Initiate EFV</td>
<td>Higher cost than NVP</td>
</tr>
<tr>
<td>WOCBP* not taking reliable contraception*</td>
<td>NVP</td>
<td>Initiate with alternative pregnancy-safe drug e.g. NLF Initiate with LPV/r</td>
<td>NLF not available in NROP and higher cost than NVP</td>
</tr>
<tr>
<td>Pregnant†</td>
<td>NVP</td>
<td>Initiate or switch to alternative pregnancy-safe drug e.g. NLF Initiate LPV/r in 2nd or 3rd trimester Initiate EFV in 2nd or 3rd trimester</td>
<td>Drug with limited experience in pregnancy and higher cost than NVP</td>
</tr>
</tbody>
</table>

* N.B. Currently the South African national roll-out programme does not recommend ART for women with a CD4 cell count of > 200/µl, but many other guidelines recommend treatment initiation at CD4 < 350 cells/µl.

† N.B. Women receiving MTCT prophylaxis may already be on ART with higher CD4 counts and in the developed world > 50% of MTCT is initiated in women with CD4 > 350 cells/µl

NVP = nevirapine; EFV = efavirenz; NLF = lornafen; LPV/r = lopinavir/ritonavir; WOCBP = women of child-bearing potential; NROP = South African national roll-out programme

References


Private-sector caesarean sections in perspective

Alan D Rothberg, Heather McLeod

In a recent issue of the Journal,1 views were expressed that our national private sector caesarean section (CS) rate is too high at over 60%, and government and/or funders are likely to intervene unless doctors begin to self-regulate by developing appropriate protocols and guidelines. This is not a new issue, but might be unreasonably and unnecessarily influenced by their doctor’s bias.1 Overseas research does not consistently support this contention; in fact several recent studies show that the overwhelming majority of obstetricians favour vaginal delivery. However the data further indicate that most obstetricians recommend CS on the basis of their patient’s right to choose a health intervention that may not be medically necessary.

Is the concern around health or costs?

We contend that this is not primarily about maternal and child health or about exposure to unnecessary anaesthetic and operative risk, because if the country was truly concerned about such matters we would have acted long ago to reduce costs of cosmetic surgery. In general we accept a patient’s right to undergo procedures such as breast reduction, augmentation and liposuction, but deal with them on the basis of the patient’s right to choose such matters we would have acted long ago to reduce costs of cosmetic surgery. In general we accept a patient’s right to undergo procedures such as breast reduction, augmentation and liposuction, but deal with them on the basis of the patient’s right to choose a health intervention that may not be medically necessary.

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