

# HATiP

HIV & AIDS Treatment in Practice

Issue 136 | Thursday, May 07, 2009



## In this issue:

### **Switching from efavirenz to nevirapine in women with higher CD4 counts; by Theo Smart and Keith Alcorn *page 2***

- ART options for pregnant women
- New findings on the safety of switching to nevirapine at higher CD4 counts
- Results
- Nevirapine's safety record
- Switching studies
- Efavirenz exposure in pregnancy and birth defects
- Expert opinion
- Implications
- Reviewers

## Switching from efavirenz to nevirapine in women with higher CD4 counts

By Theo Smart and Keith Alcorn

### Key points

- Switching from efavirenz to nevirapine may be necessary for women who wish to become pregnant or who learn that they are pregnant, or after a course of TB treatment during which efavirenz-based antiretroviral therapy was prescribed.
- Efavirenz has the potential to cause birth defects and its use is not recommended for women of childbearing potential, nor during pregnancy (especially the first three months).
- Nevirapine is not recommended for men with a CD4 count above 400 or women with a CD4 count above 250 who are new to treatment, due to a substantially higher risk of serious, life-threatening adverse reactions to the drug in these people.
- The safety of switching from another drug to nevirapine in women with CD4 counts above 250 is unclear. There is some evidence that the risk of serious adverse reactions after switching to nevirapine is lower in people who started their first antiretroviral treatment with a very low CD4 count, and in those who have undetectable viral load at the time of the switch.
- Most of the evidence comes from studies in Caucasians (whites) and there is evidence that genetic factors play a role in a person's risk of serious adverse reactions to nevirapine. More evidence is needed from other ethnic groups and from resource-poor settings.
- A new South African study found no difference in the rate of discontinuation when comparing women who started nevirapine with a CD4 count below 250 and women who switched to nevirapine from efavirenz with a CD4 count above 250.
- These findings need to be considered alongside evidence about the risk of birth defects as a result of efavirenz exposure in pregnancy.
- Efavirenz is a category D drug, which means that there is positive evidence of foetal harm as a result of exposure. This is based on five cases of brain or serious nervous system defects in infants.
- Analysis of larger datasets of women and infants exposed to efavirenz in pregnancy shows no significant difference in the rate of birth defects compared to the general population.
- Birth defects are most likely to occur as a result of drug exposure during the first three months of pregnancy.

The neural tube defects associated with efavirenz are most likely to occur as a result of exposure in the first month of pregnancy.

- Most pregnancies are not detected until at least one month after conception. Switching to nevirapine after this point may not protect against birth defects, and needs to be balanced against the risk of serious adverse events caused by nevirapine.
- It is essential that treatment programmes using efavirenz incorporate family planning services in order to manage more effectively the problem presented by efavirenz exposure during the first trimester.
- An Antiretroviral Therapy Pregnancy Registry for Africa is needed in order to provide more information about the risk of birth defects as a result of efavirenz exposure. This need will become more pressing as efavirenz becomes cheaper and more widely used.
- Women who switch to nevirapine should be closely monitored for rash, nausea or fever, especially those who switch when they have a higher CD4 count.

### ART options for pregnant women

Fixed-drug ART combinations containing nevirapine are the most commonly used among women in resource-limited settings where treatment usually begins after the CD4 cell count falls below 200. However, there are some situations, such as when a woman needs TB treatment containing rifampicin (which interacts with nevirapine) where she might be placed onto an efavirenz-based regimen. (The use of efavirenz-based regimens is likely to grow as the price falls.)

Subsequently, however, women who are doing well on treatment may wish to have children. In addition, many programmes would like to begin putting pregnant women with HIV on ART — regardless of their CD4 cell count — since it can achieve even lower rates of mother to child HIV transmission than short course AZT or single dose nevirapine.

But in these settings, the treatment options for pregnant women with higher CD4 cell counts are limited. Most do not want to take an efavirenz-based regimen because of data (in animals and a few events in people) suggesting that it can cause birth defects. Although observational data haven't identified many negative outcomes in children born to women who became pregnant on efavirenz and continued taking it, there will probably never be a definitive answer.

"A randomised controlled study of the teratogenicity of efavirenz can never be undertaken. It's just impossible that any of us who have had kids would take a drug that would potentially damage our children — it's just not going to happen," said Dr Francesca Conradie of Helen Joseph Hospital, Johannesburg, who co-chaired a symposium at the Fourth South African AIDS Conference at which new data on the safety of switching were presented (see below).

Other options, such as boosted protease inhibitor-based ART are more expensive.

That leaves nevirapine. However the package insert for nevirapine contains a black box warning against the initiation of nevirapine in patients with a high CD4 count.

Although single dose nevirapine has been shown to be quite safe, prolonged treatment is sometimes associated with rash and liver enzyme elevations. However, a small proportion of people develop allergic hypersensitivity reactions with fever, severe rash,

Stevens-Johnson Syndrome (SJS), toxic epidermal necrolysis and severe liver toxicity. According to one early meta-analysis, symptomatic hepatic events were seen in 4.9% of people taking nevirapine, while SJS is much less common.<sup>1</sup>

Symptoms generally appear within the first couple of months on treatment and usually stop if nevirapine is discontinued soon enough, but in some people fulminant hepatitis can lead to liver failure and death despite stopping drug and close monitoring.

Boehringer Ingelheim, which developed nevirapine, warned in 2004 that the risk of these severe events appeared to be greater in men with CD4 cell counts above 400, and women with a CD4 cell count above 250. The warning was based on a meta-analysis of nevirapine clinical trials and post-marketing surveillance.

In women, the risk of severe hepatotoxicity increased around twelve-fold when their baseline CD4 cell count was over 250, and this included some deaths.<sup>2</sup> When similar reactions occurred in people without HIV who were taking nevirapine as part of a month long course of post-exposure prophylaxis, it seemed to bolster the theory that people with well-preserved immune function were more at risk.<sup>3</sup>

There is a substantive body of evidence suggesting that the greater risk of severe hepatitis or hypersensitivity to women, especially pregnant women who start ART with high CD4 cell counts is quite real. However, studies have found variable rates of adverse events in different populations, so ethnicity and background incidence of viral hepatitis may be important factors. More recent studies suggest that people who experience increases in their CD4 cell counts after initiating ART can safely change therapy to a nevirapine-based regimen. But the success of this approach may depend on whether the patients had a low nadir CD4 cell count before originally going onto ART, and whether viral load is suppressed at the time of switching.

The question of nevirapine's safety in women with CD4 counts above 250 continues to raise operational questions for treatment programmes in sub-Saharan Africa and Asia.

This article reviews recent findings on the question of switching, and also reviews the evidence on the risk to the foetus of efavirenz exposure during the first trimester.

### New findings on the safety of switching to nevirapine at higher CD4 counts

Contrary to black box warnings of an increased risk of serious adverse events associated with starting on a nevirapine-based antiretroviral therapy (ART) regimen in women when CD4 cell counts are above 250, a study from Khayelitsha, South Africa has found that the rate of treatment discontinuation due to adverse events was no greater in women with high CD4 cells who switched from an efavirenz- to a nevirapine-based regimen than in those who started on nevirapine-based regimens with very low CD4 cell counts.

The study, presented at the 4<sup>th</sup> South African AIDS Conference last month in Durban, could have important implications for women who wish to become pregnant on ART or who want to take ART during pregnancy, according to Dr. Funeka Bango, who presented the paper on behalf of colleagues from the provincial government of the Western Cape, the University of Cape Town and MSF.<sup>4</sup>

Dr Bango indicated that a number of recent studies had suggested that pretreated subjects who start nevirapine have fewer side effects [these studies are described later in the article] but there had yet to be a switching study in an African population. So she and her colleagues in the Western Cape compared the probability of discontinuation between treatment experienced women in Khayelitsha who switched to nevirapine with 'high' CD4 counts over 250 (n=99) and ART-naïve women who were initiated

on nevirapine at a low CD4 count (n = 2483) between May 2001 and August 2007.

Many of the women in the high CD4 group wanted to switch from efavirenz to nevirapine because they were pregnant or wanted to become pregnant.

Two outcomes were assessed, time to 1) discontinuation due to intolerance, which would have been increase in ALT or a rash, and 2) any discontinuation (for patient reasons, hospitalisation, intolerance due to any of the antiretrovirals).

There were some significant differences in the baseline characteristics of the two groups, most of which seemed due to the fact that most of the women who started on efavirenz treatment did so because they were also being treated for TB (~64.7%). The treatment-experienced women thus had lower nadir CD4 cell counts (102 range 43-150 vs. 127 (range 71-173); slightly higher baseline viral loads, 5.2 vs. 5.0 log copies/ml; more had WHO stage IV disease; and they generally weighed less. The women switching to nevirapine were also a couple years younger (as one might expect in women becoming pregnant).

Before switching, the women had spent 18.3 months on efavirenz (range 12.2-26.4). At the point of substituting efavirenz for nevirapine, the average CD4 count was 387; and 92.7% of the women at substitution had undetectable viral loads.

### Results

The time to discontinuation and rates of discontinuation were very similar in both groups of women. For any discontinuation, a slightly higher proportion discontinued treatment in the treatment-naïve group, 24.3% (604/2483) with a higher rate of discontinuation, 18.6 per 100 person years (95% CI, 17.2 - 20.1) compared to 20.2% (20/ 99) and 16.7 per 100 person years (95% CI, 10.7 - 25.8), respectively, in the treatment-experienced group. (Dr Bango noted, though, that the latter confidence interval was rather wide).

Adverse events were very uncommon among the women who switched to nevirapine. Only 2% had hepatotoxicity; vs 1.8 percent in the LOW group had hepatotoxicity. Perhaps even more striking, there were no discontinuations in the treatment-experienced group due to rash; while 25 (1%) of the women who started nevirapine when they had low CD4 cell counts quit due to rash.

Overall, the event rate was 1.6 per 100 person years (95% CI, 0.4 - 6.4) in the treatment-experienced group versus 1.9 per 100 person years (95% CI, 1.5 - 2.4) in the treatment-naïve group.

Looking at the probability of discontinuation over time, there wasn't much difference between the two groups. However, the probability of discontinuation due to any reason increased steadily over time, while the risk for discontinuation for intolerance was higher in the first three to six months and then it leveled off.

On multivariate analysis the adjusted hazard ratios between the treatment-experienced and the treatment-naïve groups were:

- 0.73 (95% CI: 0.46 - 1.15) for any discontinuation;
- 0.72 (95% CI: 0.17 - 3.00) for intolerance;
- 0.99 (95% CI: 0.23 - 4.15) for hepatotoxicity.

"We found that low CD4 counts and weights of less than 50 kg were associated with increased risk of discontinuation. We also found that higher age was associated with increased risk of discontinuation, particularly due to intolerance," said Dr Bango.

"The findings are consistent with existing literature, suggesting there is no increased risk of discontinuation when starting nevirapine in ART-experienced patients with high CD4 counts," said Dr Bango. **"But due to the small sample size of women in the high CD4 group, the recommendation is for the study to be repeated with a larger sample size."**

### Nevirapine's safety record

The conclusions of the Khayelitsha study should be looked at in the context of what other studies have reported on the safety of using nevirapine in women.

Some of the events that contributed to a black box warning against using nevirapine in people with high CD4 cell counts (>400 in men, and >250 in women) came from a study conducted in South Africa, where the nevirapine-containing arm had to be shut down because of the high occurrence of liver toxicity (17% for the entire population and 20% in the women on nevirapine), including liver failure leading to the deaths of two women.<sup>5</sup> Although the association with higher CD4 cell counts was not found in this study, the mean baseline CD4 cell count in the study was 398, and everyone who entered the study had a CD4 cell count above 200.

Likewise, [enrolment was suspended into Pediatric AIDS Clinical Trials Group Protocol 1022](#), which recruited mostly African-American and Hispanic women, because of greater than expected toxicity, with treatment-limiting events in five out of 17 women.<sup>6</sup> One woman taking nevirapine developed Stevens-Johnson syndrome, two women experienced an increase in ALT accompanied by symptoms of hepatitis, another woman's ALT increased without symptoms, and the fifth, a 33 year old African-American woman, experienced liver failure and died. Aside from her pregnancy, there were no other risk factors for hepatitis such as hepatitis B or C. All of these women had baseline CD4 cell counts above 250.

Questions were raised as to whether the risks might be greater among women of African origin. But an observational study in the US that included 170 patients, 86% of whom were African-American (80% with CD4 counts above 250) could find no clear association.<sup>7</sup> Eleven (6.5%) patients (including 3 non-black women) developed nevirapine toxicity that required stopping the medication. In a logistic regression analysis, nevirapine toxicity was significantly associated only with having a baseline CD4 count above 250.

But outside North America, reports of toxicity have been much more variable. Reports from Thailand are on the high side, with 15.9% hepatotoxicity (4.2% leading to discontinuation) and 16.1% rash (6.8% leading to discontinuation) reported in one study of 409 adults, even though most had CD4 cell counts below 250.<sup>8</sup> But the study also included 142 pregnant women taking ART for PMTCT (with a baseline CD4 count of 413.5) who had five times the rate of nevirapine toxicity (of both rash and hepatotoxicity) as 102 pregnant women who qualified for ART for their own health (with a baseline CD4 cell count of 135.5).

In Mozambique, investigators from the DREAM programme declared nevirapine to be 'safe,' after conducting a retrospective review of clinic records from 703 HIV-positive pregnant women treated with a nevirapine-containing ART. Over the course of follow-up, grade 3-4 adverse reactions (hepatotoxicity, skin rashes and Stevens-Johnson syndrome) were reported in 6.5, 2.4 and 1.1% respectively.<sup>9</sup> Although five women died during the study, there was only evidence linking one of the deaths with nevirapine – but they didn't really know what the other women died of. It should also be noted that the study had a high maternal drop-out rate, pre- and postpartum, of 21.5% – which would leave the door open for significantly underestimating adverse events.

Eighty-one per cent of the women in the DREAM cohort had CD4 cell counts above 250 but except for the fact that hepatic toxicity was observed earlier in the subjects with higher CD4 cell counts, the investigators concluded that there was no association between CD4 cell counts and toxicity overall. However, women with higher CD4 cell counts only began ART at the 27<sup>th</sup> week of gestation, and

continued for a maximum of six months while breastfeeding (median around 4 months), while the women with lower CD4 cell counts continued on nevirapine, and thus had a much longer time to accumulate adverse events on follow-up (out to 27 months). And it isn't clear whether adverse events that develop later in advanced patients are even part of the same nevirapine-related hypersensitivity phenomenon.

A subsequent prospective study in Mozambique reported that severe hepatotoxicity was once again seen only in pregnant women with baseline CD4 cell counts over 250.<sup>10</sup> 146 pregnant women were put on a nevirapine-based regimen, about 46% of whom had CD4 cell counts between 250-350. Any toxicity (grade I-IV) involving the skin or liver was observed in 39% of participants, with 6% needing to switch regimens. Seven (5%) had grade II hepatotoxicity, and four (3%) had severe (grade III or IV) hepatotoxicity. The rate of severe liver toxicity in women with baseline CD4 cell counts between 250-350 was 6% ( $p = 0.02$ ); and a greater proportion of women with higher CD4 cells also developed SJS though this did not reach statistical significance.

There are also mixed data from Brazil, where much lower rates of severe nevirapine toxicity among pregnant women have generally been reported. Joao et al reported very low rates of toxicity in 192 subjects, with only one case of Stevens-Johnson syndrome, and one grade IV liver toxicity – but the mean duration of nevirapine exposure in this retrospective cohort was only 19.5 days.<sup>11</sup> In another study, Kondo et al reported adverse events in four of 31 women with CD4 counts below 250 (12.9%) and 23 of 102 women with CD4 counts above 250 (22.5%).<sup>12</sup> Most of the events were cutaneous, but all six (5.5%) who experienced hepatotoxicity had pretreatment CD4 counts above 250. Only two were grade III and did not become symptomatic. However, investigators discontinued nevirapine in all women with grade II/III liver toxicity and hospitalised them for observation.

In neighbouring Argentina there was a higher rate of serious adverse events, according to a retrospective study of 879 patients from Buenos Aires (533 men, 346 women, including 119 who were pregnant) presented at the World AIDS Conference last year.<sup>13</sup> It should be noted that 13% of the women and 21% of the men had hepatitis B or C infection. The median CD4 cell count was 212 in men and 231 in women. At least one adverse event occurred during the first 60 days in 90% of the patients (50% in the first two weeks). This included rash that occurred in 20.8% of women, 11.44% in men ( $p < 0.001$ ) and fever in 8.67% in women, 4.88% of the men ( $p = 0.025$ ). Liver toxicity was not significantly different, seen in 3.56% of the men and 4.92% of the women. About 10.3% of the men and 15.3% of the women discontinued nevirapine due to toxicity ( $p = 0.027$ ). In a multivariate analysis, only female sex was a significant risk factor for nevirapine toxicity (hazard ratio 1.80, 95% CI 1.24-2.62,  $p = 0.002$ ). Notably CD4 cell count (pre-nevirapine) and nadir (some of these patients were pretreated) were not significant predictors.

In Europe, the data are also mixed. In one retrospective study in Ireland in 123 pregnant women taking nevirapine-based ART (88% black), eight women developed significant hepatotoxicity, including two South African women who died from fulminant hepatitis. Women who experienced more severe hepatotoxicity had higher pretreatment CD4 counts ( $P = 0.01$ ).<sup>14</sup>

Dutch researchers reported that 11 (19%) of 58 nevirapine-using pregnant women developed hepatitis, compared with 4.2% of non-pregnant women using nevirapine.<sup>15</sup> Rash was just as common in both groups. CD4 cell counts were again much higher in the

pregnant women (median 307) compared to a median of 130 in the non-pregnant women.

However, an Italian report in a few hundred patients could find no difference between men and women in the rate of nevirapine toxicity or an effect of CD4 cell counts.<sup>16</sup> The authors postulated that some of the higher rates in other settings could be due to higher rates of comorbidities such as viral hepatitis – which some studies have shown to greatly increase the risk of nevirapine-related adverse events.<sup>17</sup>

But differences in the incidence of toxicity might also be explained by inherited characteristics that appear to alter the risk of toxicity, in particular, the human leukocyte antigen (HLA) system. HLA are molecules on the surface of cells that are involved in immune recognition and, sometime, allergies. The frequency of different HLA haplotypes varies in different populations and some have been shown to affect susceptibility to disease.

One study in an Australian cohort by Martin et al, [recently reported](#) that nevirapine hypersensitivity was significantly associated with having a stronger immune status (CD4 cell % above 25%) only when people had a haplotype HLA-DRB1\*01.<sup>18</sup> [Later, clinicians in Sardinia who noticed a higher than normal rate of nevirapine related side effects](#), found that it was associated with haplotypes HLA-Cw8 and HLA-B14.<sup>19</sup> After that, Japanese researchers also reported an association with nevirapine toxicity and HLA-Cw8.<sup>20</sup>

HLA haplotypes in Africa are extremely diverse, and the frequency of different haplotypes can vary dramatically from one region or one ethnicity to the next.<sup>21,22</sup> Of note, there has been [at least one report](#) of SJS occurring in both a Ugandan HIV-infected mother and her 8-year-old son, which suggests both that nevirapine-toxicity may have a genetic basis, and that this genetic pattern is present in some African populations.<sup>23</sup>

### Switching studies

But another notable difference between the cohort described by Manfredi and Calza and other studies was that the vast majority had been treatment-experienced before going onto nevirapine. In addition to the Khayelitsha study, several other recent studies suggest that treatment-experienced people who have high CD4 cell counts have a much lower risk of toxicity when they switch to nevirapine. These included a number of small studies that explored the safety of switching from other ART regimens to a nevirapine-based regimen, either to simplify treatment or to avoid toxicities related to protease inhibitors or efavirenz.<sup>24</sup> Even so, rates still seem to vary, perhaps, again, because these studies are performed in different settings with different populations.

At the 2006 World AIDS conference in Toronto, Mocroft et al presented evidence from the EuroSIDA cohort, which included 1,571 people who had begun a nevirapine-containing regimen since 1999.<sup>25</sup> The researchers compared the rates of treatment discontinuation (for any reason) between four groups, based upon their prior treatment experience and whether they had high current CD4 cell counts (>400 for men, and >250 for women).

The risk for discontinuation was 48% in the ART-naïve/high CD4 group, lower (27%) in the ART-experienced/high CD4 group, the ART-naïve/low CD4 group (20%) and the ART-experienced/low CD4 group (27%). In a multivariate analysis, people who had high CD4 cell counts but were treatment-experienced were about half as likely to discontinue treatment (overall relative hazard [RH]: 0.56; 95% confidence interval [CI]: 0.34-0.94;  $p = 0.027$ ). But the study couldn't single out which treatment changes were made because of serious nevirapine adverse events.

However, another switching study also presented at that conference concluded that the serious adverse event rate was low.<sup>26</sup> It included 233 patients with a high CD4 cell counts (about one-third women) in Belgium. At the time of switch 159 (68.8%) men had a baseline CD4 count below 400 and 74 (73.3%) women had a baseline CD4 count above 250.

The frequency of discontinuation for rash associated with severe hepatotoxicity (ALT/AST > 5 times the upper limit of normal) was 2/233 (0.8%): 0/159 (0.0%) for men and 2/74 (2.7%) for women. Discontinuation for rash (mild, moderate or severe) alone was 21/233 (9.0%): 10/159 (6.3%) for men and 11/74 (14.9%) for women. The frequency of discontinuation for severe hepatotoxicity was 6/233 (2.6%): 3/159 (1.9%) for men and 3/74 (4.0%) for women. Meanwhile, a retrospective German study conducted including 507 treatment-naïve and -experienced patients treated at a single centre in Munich, concluded that gender and CD4 cell counts did not affect toxicity.<sup>27</sup>

Then [a small prospective study](#) from Chennai, India in 36 treatment-experienced people (42% women) reported no cases of severe hepatotoxicity whatsoever for at least a year after switching from efavirenz to nevirapine-based therapy.<sup>28</sup> The median baseline CD4 cell count had been 162, but was around 463 at the time of switch. Liver function did not change significantly in the twelve months after switching to nevirapine. In fact, the proportion of patients with elevated liver enzymes fell during follow up.

Two separate meta-analyses have since tried to pool some of the studies to look at the safety and effectiveness of switching. De Lazzari et al evaluated nevirapine toxicity in 410 virologically suppressed patients, pooled from four prospective studies (three Spanish, one Canadian).<sup>29</sup> They reported the risk of hepatotoxicity within the first three months of switching to be 2% in those with low CD4 cell counts and 4% in those with high CD4 cell counts. Using a meta-regression model, they concluded gender and CD4 cell count (or hepatitis C) did not appear to affect toxicity. However, it should be pointed out that the focus of two of these studies was rash (and the study interventions to reduce rash, prednisone and cetirizine, actually made the problem worse). This could have led to patients being censored or discontinuing treatment before liver toxicity developed on nevirapine.

Ena et al performed another meta-analysis comparing staying on a PI-based regimen to switching to a nevirapine-based regimen in 550 virologically suppressed patients from six studies (all from Spain or Italy).<sup>30</sup> At study entry, patients had a mean CD4 count above 500 in all of the trials. Overall, switching to nevirapine was tolerated just as well as staying on PI-based therapy, but there was a 7% rate of severe hepatotoxicity leading to drug discontinuation in patients treated with nevirapine. The study populations included a high proportion of injecting drug users (and hepatitis C), which might have made liver toxicity more common, so the researchers concluded “patients with hepatitis C or B virus infection should be carefully monitored to prevent severe liver toxicity or skin reactions during the treatment.”

However, hepatitis B or C virus coinfection did not independently increase the likelihood of discontinuing nevirapine treatment due to hypersensitivity reactions (HSRs; rash and/or hepatotoxicity) in the largest observational cohort study thus far, the ATHENA cohort, which included 3752 people treated with nevirapine-based regimens at 22 Dutch hospitals from 1998-2006.<sup>31</sup> Overall, 231 patients (6.2%) discontinued nevirapine because of severe toxicity – and female gender and ‘Asian’ ethnicity were independent risk factors for HSRs (Asian women had the highest risk).

The authors made a number of interesting observations about the relationship between toxicity and nadir CD4 cell count, current

CD4 cell count and viral load. Having an undetectable viral load when switching to nevirapine was associated with reduced risk of developing an HSR (adjusted odds ratio [OR], 0.52; 95% confidence interval [CI], 0.38–0.71). Treatment-experienced patients who had had a low nadir CD4 cell count, but now had a high current CD4 cell count did not have an increased risk of developing an HSR (adjusted OR, 1.03; 95% CI, 0.66–1.61), as long as their viral load was undetectable (compared to treatment-naïve people who began nevirapine with low CD4 cell counts. However, if viral load was *detectable* when someone with low pre-ART and high current CD4 cell count switched to nevirapine the risk was increased (adjusted OR, 1.87; 95% CI, 1.11–3.12).

The incidence of hypersensitivity reaction increased with higher CD4 cell counts (nadir or current), whether someone was treatment-experienced or not. The highest risk however, was seen among treatment-experienced people who began ART with high nadir CD4 counts, and had high current CD4 cell counts when they switched to nevirapine (OR 2.71 (CI 1.69–4.35),  $p < .001$ ). Having a high nadir CD4 cell count when ART started increased the risk of nevirapine toxicity, regardless of whether the current CD4 cell count was high or low

The ATHENA study **underscores the fact that it may take large numbers of patients to detect important differences in safety profiles of a drug** – and there may still be differences by ethnicity or gender that may not be entirely eliminated according to how or when someone switches to nevirapine. Being treatment-experienced may not be enough – having a low nadir CD4 cell count and an undetectable viral load may be critical. Finally, it also should be pointed out that pregnancy, which may itself be a risk factor for hypersensitivity reactions, was not specifically addressed in any of these switching studies.

Another concern is that at present, there are no data from a randomised study which can provide guidance on precisely how nevirapine should be dosed during the first few weeks of a switch. If a straightforward switch takes place from efavirenz 600mg once daily to nevirapine 200mg twice daily, the risk of rash and hepatotoxicity may be elevated – conversely, if pretreatment with efavirenz induces nevirapine metabolism, giving nevirapine at a lower loading dose for two weeks might be unnecessary and worse, lead to subtherapeutic drug levels .

Instead, some researchers have proposed a two week crossover period during which efavirenz dosing is continued to guard against sub-optimal nevirapine concentrations, while taking a 200mg once-daily induction dose of nevirapine. Clinicians at Birmingham Heartlands Hospital evaluated this approach prospectively in a very small study of 13 patients switching from efavirenz to nevirapine, using therapeutic drug monitoring, and observed adequate drugs levels and no adverse events.<sup>32</sup>

### Efavirenz exposure in pregnancy and birth defects

The data on the risk of switching to nevirapine at CD4 counts above 250 also need to be considered in relation to what is known about the risk of adverse outcomes in infants exposed to efavirenz during pregnancy.

The Antiretroviral Therapy Pregnancy Registry in the United States enrolls about 900 pregnant women each year who have been exposed to antiretroviral drugs during pregnancy, and has analysed data accumulated between 1989 and 2008, and also includes data on 2106 pregnancies in the Women and Infants Transmission Study and 72 pregnancies from a Botswana series.<sup>33</sup> In its most recent report the authors concluded that, based on 364 live births in women exposed to efavirenz during pregnancy, no elevated risk of birth defects could be detected (2.7% prevalence (95% confidence

interval 1.3% - 5%) . The study is powered to detect a twofold increased risk of birth defects in infants born to efavirenz-exposed mothers.

However it is important to note that in 2005 the US Food and Drug Administration [issued a warning](#) about the risk of foetal harm if exposed to efavirenz, especially during the first trimester, based on 207 fetuses, and downgraded efavirenz from a category C to category D drug, indicating positive evidence of foetal risk. Five birth defects were noted in 188 fetuses exposed to efavirenz during the first trimester (5.6% prevalence), compared to none of 13 infants exposed during the second or third trimester. Four neural tube defects were reported: three cases of meningomyelocele and one of Dandy Walker Syndrome. These cases are included in the Antiretroviral Pregnancy Registry analysis.

Subsequent publications and presentations have revisited the question of the risk attached to efavirenz exposure specifically in resource-limited settings.

A prospective study in Botswana comparing first-line antiretroviral regimens reported on the outcomes of 71 pregnancies among 451 women enrolled in the study, a rate of 7.9 per 100 person-years (lower than the 11% rate seen in the general population).

The study found a high rate of early pregnancy loss (42%), but this did not differ between efavirenz exposed women and others, and was probably attributable to abortion, the investigators said. Thirty-eight of 71 women were exposed to efavirenz during the first trimester, resulting in 22 live births. There was no difference in rate of still birth between efavirenz-exposed women and others (3%), and only one birth defect (right limb shortening). The investigators concluded that this was not related to efavirenz exposure since efavirenz was discontinued 31 days after the mother's last period, before gestation reached the point at which limb development would be expected to occur.<sup>34</sup>

The investigators noted that because of the wide range of contraindications to nevirapine use, **it is essential that treatment programmes using efavirenz incorporate family planning services in order to manage more effectively the problem presented by efavirenz exposure during the first trimester.** Many of the pregnancies recorded in the study were unwanted, they discovered. WHO guidelines state that the benefits of efavirenz may outweigh the risks for women who have efficient contraception.

Theresa Russouw and colleagues at the University of Pretoria, South Africa, reviewed data on 37 women exposed to efavirenz during pregnancy at their treatment centre between 2002 and 2007. No birth defects were noted, and the proportion of infants with a low birth weight (11%) was below the provincial average (18%). No other adverse obstetric outcomes were noted.<sup>35</sup>

The limitations of both these series, as the authors note, are the small sample sizes. A larger sample, addressing two efavirenz exposure categories, provides somewhat reassuring data. Dr Ebrahim Bera of Frere Hospital, East London, Eastern Cape, reported on infant outcomes among women exposed to efavirenz in either the first or second trimester of pregnancy between January 2006 and November 2008.<sup>36</sup>

One hundred and eighty women were exposed to efavirenz in the first trimester of 205 pregnancies (some fell pregnant more than once while taking efavirenz). Although termination of pregnancy is routinely offered by the clinic to all women who become pregnant while taking efavirenz, only three opted for termination. Fifty-one switched to nevirapine and eight to lopinavir/ritonavir. One hundred and twenty three women were exposed to efavirenz throughout the first trimester of pregnancy, and presumably, continued to take the drug throughout pregnancy. The rate of birth defects was 3.6% in

infants exposed to efavirenz in the first trimester (six cases), and all were of questionable association to efavirenz. No neural tube defects were seen, and multivariate analysis could detect no risk factor significantly associated with birth defects.

At Frere Hospital women who had progressed beyond week 14 of gestation and who needed ART for their own health were offered efavirenz-based ART after an ultrasound examination of the foetus, and provided that they gave a written undertaking to use contraception postpartum (in order to avoid inadvertent exposure of another foetus to efavirenz during the first trimester).

In 568 women exposed in the second trimester (those who commenced efavirenz-containing ART after the first trimester), 14 birth defects were observed in 570 live births (2.5% prevalence). Again, no neural tube defects were observed (as would be expected given the lack of first trimester exposure), and the predominant defect was an extra finger or toe, a defect that is more common in people of African origin, especially males.

The authors caution that the numbers reviewed in their study are too low to draw definitive conclusions, and propose that what is needed is a South Africa-wide Antiretroviral Pregnancy Registry. The number of women exposed to efavirenz in the first trimester at one site alone in just less than three years suggest that it wouldn't take long for a South African registry to accumulate enough data to allow firmer conclusions to be drawn.

This is especially important when one considers [last month's announcement](#) by the Clinton HIV/AIDS Initiative and UNITAID of a further reduction in the price of an efavirenz-based triple combination, and recent moves by countries such as Zambia and Uganda to adopt it. Efavirenz-based ART is going to become more common, and the need to make a clinical decision about whether to switch and who to switch will become more frequent.

A review article by Matthew Chersich of the International Centre for Reproductive Health, Mombasa, Kenya, Glenda Gray and Francois Venter of the University of Witwatersrand, South Africa, and colleagues, published in 2006, which discusses the data on efavirenz teratogenicity in detail, concluded "Current recommendations for care for women who become pregnant while receiving efavirenz may need to be reconsidered, particularly in settings with limited alternative drugs and laboratory monitoring. ...In women who become pregnant while receiving EFV, a decision to temporarily suspend treatment or to substitute EFV after the period of organogenesis is unwarranted, especially in settings with limited alternative drugs." They too endorse the need for an adequately powered prospective registry of pregnant women in Africa to provide more detailed information. (The full text of the article is freely available as [a pdf here](#). It provides a thorough review of the evidence).<sup>37</sup>

In particular they note that neural tube defects, the only birth defect positively associated with efavirenz by regulators, are likely to develop within 28 days of conception, so changes to efavirenz-based regimens after this point will not prevent this defect, and changes after eight weeks of pregnancy will not prevent other structural defects.

Nevertheless, Chersich et al also wrote "For women planning a pregnancy or not using contraception, efavirenz should be avoided if alternatives are available."

### Expert opinion

Clinicians we consulted had somewhat differing views on the question of switching to nevirapine at higher CD4 counts, partly driven by their own experiences in the field.

Professor Anthony Harries said that the experience in Malawi had not raised significant concerns in a setting where CD4 counts are not routinely available.

"Probably half our patients [with] Stage 3 [disease] start nevirapine-based ART without knowing CD4 counts, and I think based on our operational research 10% have a CD4 count above 350."

Rony Zachariah, coordinator of operational research and documentation with MSF, said: "In female patients initiated on efavirenz and rifampicin and then switched to nevirapine at the end of anti-TB treatment, this goes smoothly in practice and thus the problem of high CD4 count and hepatotoxicity might be a problem associated with treatment-naive patients."

"In our frequent meetings with partners and stakeholders and in our quarterly supervisions around the country we did not hear of hepatotoxicity or skin reactions as a result of this changing therapy [in patients previously receiving efavirenz during TB treatment]. So, I think hepatotoxicity was not a major issue. However, we have no good data on this," said Professor Harries.

However, Dr Zachariah added "We are currently analysing data on all TB patients (male and females) who started NVP based ART in Thyolo and have ALT data and would gladly stratify the two to see if there is a difference. We also have CD4 counts and thus could be able to give more descriptive information among females."

Dr Annelies van Rie told HATIP she would like to perform a similar switching study in the Democratic Republic of Congo.

"I have always found this an intriguing question, and one that should be modeled to see what the benefit vs harm would be at population level," she said.

"What do you tell the woman who has been on efavirenz who wants to become pregnant? She won't want to stay on efavirenz if there is even the slightest risk it might harm her baby. Most want to switch to nevirapine if it is safe to do," Dr Francesca Conradie of Helen Joseph Hospital in Johannesburg told HATIP. "The only thing that gives me pause is that we were involved in the emivirine studies. The drug worked quite well but was discontinued by the sponsor. Afterwards, we switched the participants over to nevirapine, and quite a few women had side effects, which in one case was quite serious."

"I don't agree with the wording of conclusions of those studies that state that nevirapine is safe in women who are on ART with a CD4 count above 250," Dr Graeme Meintjes of GF Jooste Hospital, Cape Town, told HATIP.

"What these studies demonstrate is that the heightened risk associated with a high CD4 is not present if that CD4 count has risen on ART from a low baseline CD4. However this does not equate to it being safe, and putting out this message is misleading, because a minority of patients may still develop life-threatening hepatitis and skin reactions. Putting out the message that it's safe may result in less vigilance for these cases from clinicians.

"By way of example, we were referred a case last year of a woman with a CD4 above 500 on ART who was switched from efavirenz to nevirapine in primary care because of a wish to fall pregnant. Her ALT was not monitored, early symptoms of hepatitis were ignored and she was finally referred with fulminant liver failure and died. It's only one case but does illustrate the need for close vigilance in all patients who start or switch to nevirapine - regardless of CD4 count."

### Implications

The results of the South African study are very different from the reports which led to the black box warning on the nevirapine label. Even so, severe reactions to nevirapine that are relatively

uncommon may show up with a somewhat larger sample size. Furthermore, if there is some genetic basis for hypersensitivity, what is safe in Khayelitsha may not be safe in Asia, or Uganda, or possibly even other parts of South Africa. The background burden of viral hepatitis may also need to be considered.

The study's findings do indeed need to be validated in other settings and other ethnicities so that women have an accurate idea of their risk of toxicity.

**It should be stressed that the Khayelitsha findings only pertain to women who are already treatment-experienced on ART.** In addition, almost all of these women had undetectable viral loads when they switched and very low CD4 cell count nadirs before going onto efavirenz. It has not been demonstrated that switching would be as safe for women who initiated ART with higher CD4 cell counts or if they have detectable viral loads on efavirenz (in which case they should probably be switched to a protease inhibitor-based regimen anyway).

It is also worth reiterating and extending the point made by Chersich, Gray and Venter: by the time pregnancy is detected in the majority of women on efavirenz, any teratogenic effect of the drug will already have passed, so the true risk-benefit question for women in this situation is: does the risk of birth defects *after* the organogenesis period on efavirenz outweigh the risk of life-threatening toxicity when switching to nevirapine for a woman with a higher CD4 count?

**Finally, given the history of severe adverse events in pregnant women with high CD4 cell counts, it still seems prudent to monitor such patients closely with more frequent clinic or home based care visits or other community-based means of follow-up to watch for rash, nausea, or fever that occur soon after switching to nevirapine.**

## Reviewers

Professor Anthony Harries, International Union Against Tuberculosis and Lung Disease; Rony Zachariah, MSF; Dr Annelies Van Rie, University of North Carolina; Dr Graeme Meintjes, GF Jooste Hospital, Cape Town.

## References

- Dieterich DT et al. Drug-induced liver injury associated with the use of nonnucleoside reverse-transcriptase inhibitors. *Clinical Infectious Diseases* 38:S80-S89, 2004.
- Stern JO et al. A comprehensive hepatic safety analysis of nevirapine in different populations of HIV-infected patients. *JAIDS* 34(1):S21-33, 2003.
- CDC. Serious adverse events attributed to nevirapine regimens for postexposure prophylaxis after hiv exposures - worldwide, 1997-2000. *MMWR*; 51 & 52:1153-1156, 2001.
- Bango F - Is it safe to substitute nevirapine for efavirenz in women with high CD4 counts on ART? The experience from Khayelitsha. 4<sup>th</sup> South African AIDS Conference, Durban, 2009.
- Sanne I et al. Severe hepatotoxicity associated with nevirapine use in HIV-infected subjects. *JID*, 191:825-9, 2005.
- Hitti JH et al. Maternal toxicity with continuous nevirapine in pregnancy: results from PACTG 1022. *J Acq Immune Defic Syndr*36(3): 772-6, 2004.
- Gonzalez-Garcia A et al. Nevirapine toxicity in the obstetrical population when used in combination with other antiretrovirals. The XV International AIDS Conference, Bangkok, abstract no. WePeB5918, 2004.
- Phanuphak N et al. Nevirapine-associated toxicity in HIV-infected Thai men and women, including pregnant women. *HIV Medicine* 8(6): 357-366, 2007.
- Marazzi MC et al. Safety of nevirapine-containing antiretroviral triple therapy regimens to prevent vertical transmission in an African cohort of HIV-1-infected pregnant women. *HIV Medicine*. Volume 7, Issue 5, Pages 338-344, 2006.
- Jamisse L et al. Antiretroviral-associated toxicity among HIV-1-seropositive pregnant women in Mozambique receiving nevirapine-based regimens. *JAIDS* 44(4): 371-376, 2007.
- Joao EC et al. Nevirapine toxicity in a cohort of HIV-1-infected pregnant women. *Am J Obstet Gynecol*; 194:199-202, 2006.
- Kondo W et al. Nevirapine-induced side effects in pregnant women - experience of a Brazilian university hospital. *Braz J Infect Dis*.11(6), 2007.
- Bottaro E et al. Nevirapine-associated toxicity in a HIV positive cohort in Buenos Aires, Argentina. XVII International AIDS Conference, Mexico City, abstract THPE0201, 2008.
- Lyons, F et al. Maternal hepatotoxicity with nevirapine as part of combination antiretroviral therapy in pregnancy. *HIV Medicine* 7(4) 255-260, 2006.
- Timmermans S et al. Nelfinavir and nevirapine side effects during pregnancy. *AIDS*;19:795-799, 2005
- Manfredi R, Calza L. Nevirapine versus efavirenz in 742 patients: no link of liver toxicity with female sex, and a baseline CD4 cell count greater than 250 cells/ml. *AIDS* 20(17): 2233-2235, 2006.
- Nunez M, Martin-Carbonero L, Soriano V. Impact of hepatitis C virus (HCV) on morbidity and mortality rates among HIV-infected patients. *Clin Infect Dis*; 37:460-461, 2003.
- Martin A et al. Predisposition to nevirapine hypersensitivity associated with HLA-DRB1\_0101 and abrogated by low CD4+ T cell counts. *AIDS*; 19:97-99, 2005.
- Littera R et al. HLA-dependent hypersensitivity to nevirapine in Sardinian HIV patients. *AIDS* 20: 1621-1626, 2006.
- Gatnaga H et al. HLA-Cw8 primarily associated with hypersensitivity to nevirapine. *AIDS*; 21:264-265, 2007.
- Tian W et al. MICA, HLA-B haplotypic variation in five population groups of sub-Saharan African ancestry. *Genes and Immunity* 4, 500-505, 2003.
- Sanchez-Mazas A. African diversity from the HLA point of view: influence of genetic drift, geography, linguistics, and natural selection. *Hum Immunol*. 62(9):937-48, 2001.
- Liechty C et al. Nevirapine-induced Stevens-Johnson syndrome in a mother and son. *AIDS* 2005; 19:993-994, 2005
- Gatnaga H et al. HLA-Cw8 primarily associated with hypersensitivity to nevirapine. *AIDS*; 21:264-265, 2007.
- Harris M. Efficacy and durability of nevirapine in antiretroviral-experienced patients. *J AIDS* 34 (Suppl): 53-58, 2003.
- Mocroft A, Staszewski S, Weber R, et al. Risk of discontinuation of nevirapine due to toxicities in antiretroviral naive and experienced patients with high and low CD4 counts. *Antivir Ther* 12:325-33, 2007.
- De Roo A. Incidence of rash and severe hepatotoxicity in patients switching from a protease inhibitor (PI) or efavirenz (EFV) to nevirapine (NVP) at relatively high CD4 count levels. XVI International AIDS Conference, Toronto, abstract CDB0697, 2006.
- Wolf E, Koegl C, Theobald T. Nevirapine-associated hepatotoxicity: No increased risk for females or high CD4 count in a single centre HIV cohort. 46<sup>th</sup> Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC). San Francisco, abstract H-1063, 2006.
- Kumarasamy N et al. Safety of switching to nevirapine-based highly active antiretroviral therapy at elevated CD4 cell counts in a resource-constrained setting. *J Acquir Immune Defic Syndr* 45: 598-600, 2007.
- De Lazzari E et al. Hepatotoxicity of nevirapine in virologically suppressed patients according to gender and CD4 cell counts. *HIV Med*. 9(4):221-226, 2008.
- Ena J et al. Switching from suppressive protease inhibitor-based regimens to nevirapine-based regimens: a meta-analysis of randomized controlled trials. *HIV Med*. 9(9):747-756, 2008.
- Wit FWMN et al. Discontinuation of nevirapine because of hypersensitivity reactions in patients with prior treatment experience, compared with treatment-naive Patients: the ATHENA cohort Study. *Clinical Infectious Diseases* 46:933-940, 2008.
- Dufty N et al. Switching from efavirenz (EFV) to nevirapine (NVP): a novel pharmacological strategy. *HIV Medicine* 10 suppl 1: 7 (abstract 21), 2009.
- Antiretroviral Pregnancy Registry Steering Committee. Antiretroviral Pregnancy Registry international interim report for 1 Jan 1989 - 31 January 2008. Wilmington, NC: Registry Coordinating Center; Available at: <http://www.APRegistry.com>
- Bussmann H et al. Pregnancy rates and birth outcomes among women on efavirenz-containing highly active antiretroviral therapy in Botswana. *Journal of Acquired Immune Deficiency Syndromes* 45(3):269-273, 2007.

35. Roussoux T. Quantifying antiretroviral risk in pregnancy. SAMJ 97(11): 1015-1016, 2007.  
36. Bera E et al. Birth defects and perinatal outcomes from 748 pregnant women who took efavirenz as part of lifelong antiretroviral therapy. A prospective study at a tertiary hospital in South Africa. 4<sup>th</sup> South African AIDS Conference, Durban, abstract 395, 2009.

37. Chersich MF et al. Efavirenz use during pregnancy and for women of child-bearing potential. AIDS Research and Therapy 3 (11), 2006.

## about HATIP

A regular electronic newsletter for health care workers and community-based organisations on HIV treatment in resource-limited settings.

Its publication is supported by the UK government's Department for International Development (DfID), the Diana, Princess of Wales Memorial Fund and the Stop TB Department of the World Health Organization.

Other supporters include Positive Action GlaxoSmithKline (founding sponsor); Abbott Fund; Abbott Molecular; Cavid; Elton John AIDS Foundation; Merck & Co., Inc.; Pfizer Ltd; F Hoffmann La Roche; Schering Plough; and Tibotec, a division of Janssen Cilag.

The newsletter is edited by Theo Smart (Cape Town) and Keith Alcorn, NAM's Senior Editor (London).

For further information please visit the HATIP section of [aidsmap.com](http://aidsmap.com)