

# Safety of Efavirenz

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## Switch studies

### ***Reoccurrence of rash or hepatotoxicity after NNRTI switch***

A publication reviewed the safety of switching from EFV to NVP, or vice versa, in the event of a skin reaction or hepatotoxicity<sup>1</sup>. The hypersensitivity reactions occur in 4-38% of patients on NVP and 4.6-20% of patients on EFV. Of the 239 patients who were switched from NVP to EFV due to rash, 30 (12.6%, 95% CI 2.7-22.4%) had a recurrence of rash or other hypersensitivity with EFV. Of the 16 patients switched from EFV to NVP due to rash eight reported cross-reactivity (50%, 95% CI 26.7-73.3%). Severe rashes such as Stevens Johnson Syndrome, toxic epidermal necrolysis, and erythema multiforme were reported in 0.1% of EFV patients and 0.3-1% of NVP patients. Hepatotoxicity occurs in 1.4-17% of NVP patients and 1.1-8% of EFV patients. In the 2NN study, higher trough concentrations of EFV were associated with hepatotoxicity. None of the 11 patients switched from NVP to EFV due to hepatotoxicity had recurrent hepatotoxicity on EFV. A case reported a patient who was safely switched from EFV to NVP because of hepatotoxicity.

A retrospective analysis in Thailand evaluated risk factors for recurring rash in 109 patients who were switched from NVP to EFV<sup>2</sup>. 20 (18.3%) patients in this analysis developed rash with EFV and had to switch to PI based therapy. When compared to the 89 patients who did not develop a rash with EFV, there appeared to be significant associations with a history of an allergy to a drug other than NVP ( $p < 0.001$ ), a low CD4+ count at NVP initiation ( $p = 0.003$ ), and a high pVL at NVP initiation ( $p = 0.020$ ).

**Summary:** This evidence suggests that when a hypersensitivity reaction occurs with NVP it is safe to switch to EFV. Conversely, when a hypersensitivity reaction occurs with EFV it is not safe to switch to NVP.

### ***Dosing and safety when switching from EFV to NVP***

A study in Cambodia evaluated the incidence of adverse events for 394 patients who were switched from EFV to NVP 200 mg twice daily, without the recommended dose escalation of two weeks of NVP 200 mg daily<sup>3</sup>. The nucleoside backbone consisted of d4T and 3TC. The incidence of cumulative and serious adverse events was 13.2 and 8.9%, respectively. In women the incidences were slightly higher at 17.6% and 12.2%. These incidences appear to be similar to those achieved when patients are initiating NVP based cART using escalated doses.

A randomised study in England analysed whether to initiate NVP at the full or reduced dose after EFV based cART in 12 individuals<sup>4</sup>. Patients were required to be on EFV based cART for at least one month prior to the start of the study. The two treatment arms consisted of six patients on NVP 200 mg daily and six patients on NVP 200 mg twice daily. Patients on the daily dose of NVP had troughs below the recommended value of 300 ng/mL while patients on the twice-daily dose had a mean trough exceeding this threshold. pVL was undetectable in all patients three months after NVP initiation.

Summary: NVP and EFV cause autoinduction of CYP 2B6. When steady state concentrations of EFV are reached and there is a need to switch to NVP, NVP can be dosed at 400 mg daily or 200 mg BID. If there is an NNRTI free interval between the switch from EFV to NVP, the patient's ethnicity should be considered when determining whether to start at reduced or full dose NVP, as different ethnicities metabolize EFV differently (see Pharmacokinetics section below). Generally, if it has been less than two weeks then NVP should be started at the full dose while if the interval has been longer than two weeks the reduced dose should be used.

### ***Switching from EFV to NVP because of neuropsychiatric symptoms***

Patients with undetectable pVL were switched from EFV to NVP in 36 patients due to neuropsychiatric symptoms in an American retrospective analysis<sup>5</sup>. After the switch to NVP pVL remained undetectable for a median of 25 months. Of the twenty patients who reported neuropsychiatric symptoms (i.e. depression, anxiety, or fatigue with or without sleep disturbances) before the switch, fifteen experienced complete resolution after the switch to NVP.

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<sup>1</sup> Mehta U, Maartens G. Is it safe to switch between efavirenz and nevirapine in the event of toxicity? *Lancet Infect Dis.* 2007 Nov;7(11):733-8.

<sup>2</sup> Kiertiburanakul S, Malathum K, Watcharananan S, Sathapatayavongs B, Sungkanuparph S. Predicting factors for unsuccessful switching from nevirapine to efavirenz in HIV-infected patients who developed nevirapine-associated skin rash. *Int J STD AIDS.* 2009 Mar;20(3):176-9.

<sup>3</sup> Laureillard D, Prak N, Fernandez M, Ngeth C, Moeung S, Riel V, et al. Efavirenz replacement by immediate full-dose nevirapine is safe in HIV-1-infected patients in Cambodia. *HIV Med.* 2008 Aug;9(7):514-8.

<sup>4</sup> Winston A, Pozniak A, Smith N, Fletcher C, Mandalia S, Parmar D, et al. Dose escalation or immediate full dose when switching from efavirenz to nevirapine-based highly active antiretroviral therapy in HIV-1-infected individuals? *AIDS.* 2004 Feb 20;18(3):572-4.

<sup>5</sup> Ward DJ, Curtin JM. Switch from efavirenz to nevirapine associated with resolution of efavirenz-related neuropsychiatric adverse events and improvement in lipid profiles. *AIDS Patient Care STDS.* 2006 Aug;20(8):542-8.

## **Pregnancy Studies**

### ***Prospective Reports***

A prospective study in Botswana evaluated the impact of EFV on pregnancy in 451 female participants<sup>6</sup>. First trimester EFV exposure occurred in 38 of the 71 pregnancies; 22 of these 38 pregnancies resulted in live births (57.9%) while 16 resulted in abortions (42.1%). The median time of EFV exposure was 43 days (IQR: 31-60 days), all women were switched to non-EFV containing cART the same day that pregnancy was diagnosed. Among the 17 liveborn infants who were not exposed to EFV based cART, two minor congenital abnormalities were detected (one infant with polydactyly and one infant with an umbilical hernia) while there were two stillbirths. Of the 22 EFV exposed live births one infant had a major congenital abnormality that was unrelated to EFV exposure (bone dysplasia) while there were two premature births. There was no difference in median birth weight, gender, occurrence of early pregnancy loss, and stillbirths between mothers who were or were not on EFV containing cART.

The most recent antiretroviral pregnancy registry received prospective reports on 620 pregnancies exposed to EFV-containing regimens, a majority of which were first-trimester exposures (579 pregnancies)<sup>7</sup>. Birth defects occurred in 14 of 477 live births who were exposed during the first trimester (2.94%) and two of 41 live births exposed during the second or third trimester (4.89%). Defects reported in fourteen infants with first trimester exposure to EFV were: 1) polydactyly, 2) hydronephrosis, 3) bilateral hip dislocation and umbilical hernia, 4) bilateral hip dislocation, 5) urinary obstruction, duplicated right collecting system with obstructed upper pole moiety, possibly associated with vesicoureteral reflux, 6) polydactyly, and 7) long bones malformation, 8) sacral myelomeningocele and hydrocephalus with fetal alcohol syndrome, 9) shortening of right leg, 10) cutis aplasia (scalp), 11) hip dysplasia and pulmonary stenosis, 12) bilateral facial cleft, anophthalmia and amniotic band, and 13) postaxial polydactyly both hands, and 14) unspecified heart anomaly.

During the July 2008 reporting period, the Registry received a first case of anophthalmia, a defect reported in a study in monkeys. However, this case also included severe oblique facial clefts and amniotic banding, a known association with anophthalmia. This rate of defects is similar to the general population in the USA (3.1%, 95% CI 3.1-3.2%), though in 2005 the incidence of anencephaly was 11.3 per 100,000 births and meningomyelocele/spina bifida was 18.0 per 100,000 births in the USA<sup>8 9</sup>. There have been five retrospective reports on cases consistent with neural tube defects: three infants with meningomyelocele and two with a Dandy-Walker malformation. All five cases occurred to mothers who were on EFV-based cART during their first trimester.

Malformations were observed in three of 20 fetus/infants from EFV treated cynomolgus monkeys (vs. 0 of 20 unexposed monkeys) in a developmental toxicity study. Anencephaly and unilateral anophthalmia were observed in one fetus, microphthalmia was observed in another fetus, and cleft palate was observed in a third fetus. The monkeys were dosed to achieve concentrations similar to those in humans on EFV 600 mg daily. EFV crosses the placenta in monkeys, and fetus plasma concentrations are similar to those in the mother. An increase in fetal resorptions was seen in EFV exposed pregnant rats, when peak plasma concentrations and AUC values were similar to those achieved in humans on EFV 600 mg daily. No reproductive toxicities were seen in pregnant rabbits at doses that produced peak plasma concentrations similar to, and AUC values approximately half of, those achieved in humans given 600 mg daily. It is worth noting that of the 1200 known animal teratogens only 30 are teratogenic to humans<sup>10 11</sup>.

In a study from Thailand, 38 females were switched from NVP to EFV containing regimen due to toxicity after the first trimester<sup>12</sup>. There were 606 women in this study and the other 568 women stayed on NVP. The mean time of exposure was  $7 \pm 4.9$  weeks. Four infants (10.5%) were born pre-term (<37 weeks gestation) and six (15.8%) had low birth weight (<2.5 kg). All infants exposed to EFV were reported healthy at birth and no congenital anomaly was observed. These rates were not higher than the rates observed in the NVP based regimen group (18.5% pre-term birth,  $p=0.295$  and 16.0% low birth weight  $p=0.639$ ).

## ***Retrospective reports***

A retrospective analysis in France evaluated the impact of EFV exposure (average eight weeks, range 2-20 weeks) in 12 pregnant women<sup>13</sup>. Two women had miscarriages and two women had abortions. Seven infants were born. There were three abnormalities in the twelve women. One born infant had two benign angiomas in the right arm, the second developed severe hypotrophy due to placental infarction and was medically aborted, while the third infant developed multiple deformities in the pulmonary bicuspid valve, had accelerated maturation of the skeleton, and anomalies in the pulmonary circulation and was also medically aborted. There were no reports of neural tube defects.

In a retrospective study, data from seven women who received EFV during pregnancy with term delivery were examined<sup>14</sup>. Of seven infants who were born alive, five were exposed to EFV from conception and two were exposed from 12 and 14 weeks after amenorrhea. Therapy with EFV was continued in five cases and discontinued in two cases at two and four weeks gestation. The mean birth-weight for all seven newborns was 3.224 kg (2.7-4.17 kg) and Apgar score of 9-10. Clinical examination of all infants (7/7 cases) at birth and after a mean follow-up of 20.6 months (6/6 cases) was normal.

A retrospective analysis in South Africa evaluated the impact of EFV exposure in 37 women<sup>15</sup>. 15% of the women chose to have an early termination of pregnancy. There were no reports of morphological abnormalities, neural tube defects, or overt developmental delay.

Another retrospective analysis in South Africa evaluated the impact of EFV exposure in 83 women<sup>16</sup>. The mean exposure was 97.05 days (range 12-343). There were three miscarriages, one stillbirth, and 28 elective terminations.

The European Collaborative Study evaluated the risk of abnormalities in 19 mothers who were on EFV based cART<sup>17</sup>. These patients continued EFV for a median of 40 days into their pregnancy (range 24-106 days) and no congenital abnormalities (0%, 95% CI 0-17.6%) were reported.

A recent article on ARV adverse effects during pregnancy reported on EFV exposure in four pregnancies<sup>18</sup>. In two pregnancies EFV was received for a single month (one first trimester, one in third trimester), in the third patient EFV was given for the entire first trimester, and in the fourth patient EFV was given for a few days in the first trimester. There were no reported malformations or defects in these infants.

## ***Pregnancy pharmacokinetics***

A small pharmacokinetic study with 13 Rwandan women taking 600 mg of EFV once daily found that third-trimester peak levels were 61% higher than in nonpregnant individuals at that dose<sup>19</sup>.

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<sup>6</sup> Bussmann H, Wester CW, Wester CN, Lekoko B, Okezie O, Thomas AM, et al. Pregnancy rates and birth outcomes among women on efavirenz-containing highly active antiretroviral therapy in Botswana. *J Acquir Immune Defic Syndr.* 2007 Jul 1;45(3):269-73.

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<sup>7</sup> Antiretroviral Pregnancy Steering Committee Registry. Antiretroviral Pregnancy Registry International Interim Report for 1 January 1989 through 31 January 2009. Wilmington, NC: Registry Coordinating Center; 2009.

<sup>8</sup> Correa-Villaseñor A, Cragan J, Kucik J, O'Leary L, Siffel C, Williams L. The Metropolitan Atlanta Congenital Defects Program: 35 years of birth defects surveillance at the Centers for Disease Control and Prevention. *Birth Defects Res A Clin Mol Teratol*. 2003 Sep;67(9):617-24.

<sup>9</sup> Martin JA, Hamilton BE, Sutton PD, Ventura SJ, Menacker F, Kirmeyer S, et al. Births: final data for 2006. National vital statistics reports. National Center for Health Statistics 2007;57(7): 1-104. Available from: [http://www.cdc.gov/nchs/data/nvsr/nvsr57/nvsr57\\_07.pdf](http://www.cdc.gov/nchs/data/nvsr/nvsr57/nvsr57_07.pdf).

<sup>10</sup> Mills JL. Protecting the embryo from X-rated drugs. *N Engl J Med*. 1995 Jul 13;333(2):124-5.

<sup>11</sup> Chersich MF, Urban MF, Venter FW, Wessels T, Krause A, Gray GE, et al. Efavirenz use during pregnancy and for women of child-bearing potential. *AIDS Res Ther*. 2006 Apr 7;3:11.

<sup>12</sup> Phanuphak N, Apornpong T, Limpongsanurak S, Luesomboon W, Tangsathapornpong A, Singhakovinta N, et al. Pregnancy outcomes of women receiving efavirenz after the first trimester. The 14th Conference on Retroviruses and Opportunistic Infections. Los Angeles, CA 25-28 February 2007 [Abstract 745]

<sup>13</sup> Jeantils V, Khuong MA, Delassus JL, Honoré P, Taverne B, Uzan M, et al. [Efavirenz (Sustiva) in pregnancy: a study about 12 HIV patients]. *Gynecol Obstet Fertil*. 2006 Jul-Aug;34(7-8):593-6.

<sup>14</sup> Batallan A, Moreau G, Levine M, P Longuet, M Bodard, S Legac, et al. In utero exposure to efavirenz: evaluation in children born alive. 2nd International AIDS Society Conference on HIV Pathogenesis and Treatment. Paris, France 13-16 July 2003 [Abstract 1100]

<sup>15</sup> Rossouw T. Quantifying antiretroviral risk in pregnancy. *S Afr Med J*. 2007 Nov;97(11):1014, 1016.

<sup>16</sup> Laher F, Forrest J, Mohapi L, Gray G. Efavirenz Conceptions in Soweto, South Africa. The 5th IAS Conference on HIV Pathogenesis and Treatment. Cape Town, South Africa 19-22 July 2009 [Abstract 1121]

<sup>17</sup> Patel D, Thorne C, Fiore S, Newell ML. Does highly active antiretroviral therapy increase the risk of congenital abnormalities in HIV-infected women? *J Acquir Immune Defic Syndr*. 2005 Sep 1;40(1):116-8.

<sup>18</sup> Zuk DM, Hughes CA, Foisy MM, Robinson JL, Singh AE, Houston S. Adverse effects of antiretrovirals in HIV-infected pregnant women. *Ann Pharmacother*. 2009 Jun;43(6):1028-35.

<sup>19</sup> Schneider S, Peltier A, Gras A, Arendt V, Karasi-Omes C, Mujawamariwa A, et al. Efavirenz in human breast milk, mothers', and newborns' plasma. *J Acquir Immune Defic Syndr*, 2008. 48(4):450-4.

## Reduced Doses of EFV

A randomised, double-blind, study in Spain prospectively evaluated the neuropsychiatric toxicity improvements and efficacy seen using stepped versus full doses of EFV in the first two weeks of combination antiretroviral treatment (cART) in 108 treatment naïve patients<sup>20</sup>. EFV was taken in combination with two N(t)RTIs. In the stepped dose arm EFV was given at a dose of 200 mg/d from days 1-6, 400 mg/d from days 7-13, and 600 mg/d from day 14 onward. The full dose arm was given 600 mg/d of EFV from day one. After seven days of treatment neuropsychiatric side effects were more common in the full dose arm (66%) compared to the stepped dose arm (46.5%, p=0.040). Incidence rates of dizziness (66.0% vs. 32.8%, p=0.001), feeling of drunkenness or hangover (45.8% vs. 20.7%, p=0.008), impaired concentration (22.9% vs. 8.9%, p=0.038), and hallucinations (6.1% vs. 0%, p=0.056) were higher and more severe in the full-dose than in the stepped-dose group, respectively. After seven days the rates of neuropsychiatric side effects were similar in both arms. The percentages of patients receiving treatment and with undetectable pVL at weeks 4, 12, and 24 in the stepped-dose and full-dose groups were 32.1% vs. 27.7% (p=0.40), 71.2% vs. 59% (p=0.161), and 95.7% vs. 86.5% (p=0.137), respectively. Among patients with baseline viral load greater than 100 000 cp/mL (23 in the stepped-dose group and 20 in the full-dose group), these percentages at weeks 4, 12, and 24 were 5.6% vs. 5.3% (p=0.74), 52.6% vs. 35.3% (p=0.24), and 87.5% vs. 80%

( $p=0.47$ ), respectively. There were six cases of virologic failure, of which two were in the stepped-dose group and four were in the full-dose group.

A study from Japan described success in lowering daily EFV dose in 12 patients who had a polymorphism in CYP2B6<sup>21</sup>. Patients were virologically suppressed on the 600 mg/d dose for at least one month before dose reduction was made to 400mg daily. After concentrations continued to be  $>6000$  ng/mL in seven of these patients, further dose reduction to 200mg daily was made. All twelve patients maintained a pVL  $< 50$  cp/mL. A retrospective study from the Netherlands evaluated dose reduction in 187 patients who had high plasma concentrations of EFV ( $\geq 4.0$  mg/L within 48 weeks of commencing cART)<sup>22</sup>. 47 of these patients had their dose of EFV reduced to 400mg daily while the other 131 maintained standard doses of EFV. Reduced dose patients had a baseline median EFV plasma concentration [6.8 (5.7–9.6) mg/L] which was significantly higher than standard dose patients [5.1 (4.3–6.4) mg/L,  $p=0.001$ ]. 11.5 and 2.3% of the standard and reduced dose patients, respectively, discontinued EFV due to EFV toxicity ( $p=0.066$ ). Dose reduction did not impair virological response, as 95.2 and 86.1% of the reduced and standard dose patients had a pVL  $< 50$  cp/mL at week 24. Plasma concentrations remained above 1 mg/L, the minimum therapeutic Cmin, in all 42 reduced dose patients with a second measured EFV trough<sup>23</sup>.

Summary: Considering the public health approach to cART, the stepped dose study from Gutiérrez-Valencia et al. is the most relevant. Patients, regardless of their ethnicity, would experience less neurological toxicity during the first two weeks without an increased risk of virological failure. Given the limited availability of CYP genotyping and therapeutic drug monitoring dose reductions based on polymorphisms or high drug concentrations aren't relevant to most low and middle income countries.

<sup>20</sup> Gutiérrez-Valencia A, López-Cortés LF, Viciano P, Palacios R, Ruiz-Valderas R, Lozano F, et al. Stepped-Dose vs. Full-Dose Efavirenz for HIV Infection and Neuropsychiatric Adverse Events: A Randomized Trial. *Ann Intern Med.* 2009 Jul 6. [Epub]

<sup>21</sup> Gatanaga H, Hayashida T, Tsuchiya K, Yoshino M, Kuwahara T, Tsukada H, et al. Successful efavirenz dose reduction in HIV type 1-infected individuals with cytochrome P450 2B6 \*6 and \*26. *Clin Infect Dis.* 2007 Nov 1;45(9):1230-7.

<sup>22</sup> van Luin M, Gras L, Richter C, Ende ME, Prins JM, Wolf FD, et al. Efavirenz Dose Reduction Is Safe in Patients With High Plasma Concentrations and May Prevent Efavirenz Discontinuations. *J Acquir Immune Defic Syndr.* 2009 Jul 10. [Epub ahead of print]

<sup>23</sup> la Porte CJ, Back DJ, Blaschke T, Boucher CAB, Fletcher CV, Flexner C, et al. Updated guideline to perform therapeutic drug monitoring for antiretroviral agents. *Rev Antivir Ther.* 2006;3:4–14.

## EFV and anti-TB therapy

### ***Virological suppression of NVP vs. EFV with rifampicin containing anti-TB therapy***

A prospective cohort analysis from South Africa compared NVP and EFV virological outcomes when coadministered with rifampicin containing anti-TB therapy<sup>24</sup>. There were 1074 patients who were started on EFV based cART and anti-TB therapy compared to 209 started on NVP based cART and anti-TB therapy. Patients started on NVP and anti-TB therapy were at an increased risk of pVL  $> 400$  cp/mL at six months (16.3%)

compared to those who were on NVP and not on anti-TB therapy (8.3%, adjusted OR 2.1, 95% CI 1.2-3.4). When analysing confirmed virological failure, i.e. two consecutive pVL > 5000 cp/mL, patients on NVP and anti-TB therapy failed therapy sooner than patients on NVP alone (adjusted HR 2.2, 95% CI 1.3-3.7). Patients on EFV and anti-TB therapy were at no increased risk compared to patients on EFV alone (adjusted HR 1.1, 95% CI 0.6-2.0).

A prospective randomised study from Thailand compared NVP and EFV virological outcomes after twelve weeks in 142 patients on concomitant anti-TB therapy<sup>25</sup>. At week 12, 3.1% of patients in the EFV group and 21.3% of patients in the NVP group had NNRTI concentrations, after 12 hours, that were lower than the recommended minimum concentrations (OR 8.396, 95% CI 1.808-38.993, p=0.002). These low concentrations did predict all-cause treatment failure (p=0.042). However, intention to treat analysis revealed that 73.2 and 71.8% of patients in the EFV and NVP groups, respectively, achieved pVL < 50 cp/mL by week 48.

A retrospective analysis in Botswana compared the safety and efficacy of NVP and EFV based cART in 155 patients who were on anti-TB therapy<sup>26</sup>. After one year of cART there was no difference in virological outcomes between the two groups. There was a trend toward more hepatotoxic events in the TB treatment group as compared to the cART only group (9% vs. 3%, p=0.05).

### ***EFV dosing pharmacokinetics with rifampicin containing anti-TB therapy***

A prospective cohort including 20 South African patients assessed EFV 600 mg daily, as part of cART, when in combination with six months of rifampicin containing anti-TB therapy<sup>27</sup>. There was high EFV concentration variability (CV) with rifampicin, as the coefficient of variability was 157% on and 58% off rifampicin therapy. However, intra-subject levels were relatively consistent over time (CV=24%). The geometric mean efavirenz concentration was 1730 ng/mL on and 1377 ng/mL off rifampicin (p=0.55). The therapeutic range was defined as 1000-4000 ng/mL<sup>28</sup>. Seventeen of the 20 patients finished anti-TB therapy and 16 had an undetectable pVL by the end of the study. The three other patients remained viraemic, two with 3TC and EFV resistance mutations. Nineteen patients were cured of TB. Seven patients (35%) reported dizziness and poor concentration during the first few weeks after initiation of EFV therapy.

A prospective pharmacokinetic cohort evaluated the relevance of C<sub>min</sub> and antiretroviral efficacy in 48 Spanish patients who were on rifampicin containing tuberculosis therapy and EFV 800 mg daily containing cART<sup>29</sup>. Trough values obtained with 800 mg of EFV and rifampicin were similar to those achieved with 600 mg of EFV without rifampicin (1.39 vs. 1.28 ug/mL, respectively). Eight patients experienced virological failure, which was not related to EFV trough concentrations but irregular adherence. Tuberculosis was cured in all patients.

A prospective cohort from England evaluated EFV levels in nine patients on 800 mg of EFV daily with rifampicin containing TB treatment<sup>30</sup>. High EFV levels (median 11 680

ng/mL, while the therapeutic range is 1000 - 4000 ng/mL) and toxicity were seen in seven of the nine patients. Toxicity included six cases of CNS toxicity and one case of hepatitis.

**Summary:** EFV can be dosed at 600 mg daily with rifampicin containing anti-TB therapy, without an increased risk of treatment failure. NVP concentrations decrease with rifampicin, and this may result in compromised viral suppression. When availability permits, EFV should be used rather than NVP with rifampicin containing anti-TB therapy.

<sup>24</sup> Boulle A, Van Cutsem G, Cohen K, Hilderbrand K, Mathee S, Abrahams M, et al. Outcomes of nevirapine- and efavirenz-based antiretroviral therapy when coadministered with rifampicin-based antitubercular therapy. *JAMA*. 2008 Aug 6;300(5):530-9.

<sup>25</sup> Manosuthi W, Sungkanuparph S, Tantanathip P, Lueangniyomkul A, Mankatitham W, Prasithsirskul W, et al. A randomized trial comparing plasma drug concentrations and efficacies between 2 nonnucleoside reverse-transcriptase inhibitor-based regimens in HIV-infected patients receiving rifampicin. *Clin Infect Dis*. 2009 Jun 15;48(12):1752-9.

<sup>26</sup> Shipton LK, Wester CW, Stock S, Ndwapi N, Gaolathe T, Thior I, et al. Safety and efficacy of nevirapine- and efavirenz-based antiretroviral treatment in adults treated for TB-HIV co-infection in Botswana. *Int J Tuberc Lung Dis*. 2009 Mar;13(3):360-6.

<sup>27</sup> Friedland G, Khoo S, Jack C, Lalloo U. Administration of efavirenz (600 mg/day) with rifampicin results in highly variable levels but excellent clinical outcomes in patients treated for tuberculosis and HIV. *J Antimicrob Chemother*. 2006 Dec;58(6):1299-302.

<sup>28</sup> la Porte CJ, Back DJ, Blaschke T, Boucher CAB, Fletcher CV, Flexner C, et al. Updated guideline to perform therapeutic drug monitoring for antiretroviral agents. *Rev Antivir Ther*. 2006;3:4-14.

<sup>29</sup> Lopez-Cortes LF, Ruiz-Valderas R, Ruiz-Morales J, Leon E, de Campos AV, Marin-Niebla A, et al. Efavirenz trough levels are not associated with virological failure throughout therapy with 800 mg daily and a rifampicin-containing antituberculosis regimen. *J Antimicrob Chemother*. 2006 Nov;58(5):1017-23.

<sup>30</sup> Brennan-Benson P, Lyus R, Harrison T, Pakianathan M, Macallan D. Pharmacokinetic interactions between efavirenz and rifampicin in the treatment of HIV and tuberculosis: one size does not fit all. *AIDS*. 2005 Sep 23;19(14):1541-3.

## **Safety studies of EFV from low and middle income countries**

In a prospective cohort analysis of d4T/ddI/EFV therapy in Senegal, twelve patients reported neuropsychiatric symptoms (primarily dizziness) during the first month of therapy.<sup>31</sup> These symptoms resolved in all twelve patients after a median of nine days.

A retrospective cohort analysis in Senegal evaluated the efficacy and tolerance of EFV based cART in 170 patients<sup>32</sup>. There were four cases of neurological disorders in these patients which required an EFV switch.

A South African cohort prospectively analysed the safety of AZT/3TC/EFV in 853 patients, of whom 98% were male<sup>33</sup>. Five of these patients had a regimen change due to neurocerebellar changes while six changed due to liver enzyme elevations. 187 individuals (incidence 37 episodes per 100 person-years; 95% CI 32-43) developed neurocerebellar symptoms, 11 of whom had grade 3 symptoms, most frequently at week two. Subjects receiving co-trimoxazole had a higher rate of neurocerebellar symptoms (HR 1.7; P<0.001).

A cohort in Côte d'Ivoire retrospectively analysed the efficacy and tolerability of EFV+2NRTIs in 142 patients<sup>34</sup>. 39% of patients in this cohort reported neuropsychiatric disorders (i.e. vertigo with impaired sensation, headache, insomnia). These reports began in the first month and subsided over time.

A prospective analysis in West Africa analysed the tolerance of six months of AZT/3TC/EFV in an HIV/HBV coinfecting cohort of 740 patients, of whom 74% were female<sup>35</sup>. There were 9 episodes of EFV induced adverse events, including 5 neurologic events (4 episodes of severe dizziness and one episode of acute delirium), 3 cutaneous events (two episodes of intolerable pruritis and one episode of febrile rash) and one episode of grade 3 cytolytic hepatitis. The incidence of milder neurologic adverse events (i.e. insomnia, vertigo, or nightmare) after 1, 2, 3, 4, 5, and 6 months were 73%, 36%, 29%, 25%, 21%, and 17% respectively. One woman was on EFV for eight weeks into her pregnancy in this study before being switched to NFV based therapy, the delivery was normal and no malformations were detected.

An Asian cohort retrospectively analysed EFV safety in 735 patients<sup>36</sup>. 241 of these patients discontinued therapy, 10 of whom discontinued due to rash and hypersensitivity while four discontinued due to hepatotoxicity. The rates of rash as reason for treatment discontinuation were 0.7, 0.9, 0.0, and 0.0 per 100 person-years for patients of Chinese, Thai, Indian, Filipino, and other ethnicity, respectively (p = 0.99).

A prospective cohort analysis of 141 patients initiated on TDF/FTC/EFV in India reported that sixteen patients had grade 1-2 self-limiting neuropsychiatric effects while one patient had a grade 4 CNS disturbance which necessitated treatment discontinuation<sup>37</sup>.

The efficacy and toxicity of AZT/3TC/EFV was prospectively analysed in a cohort of 428 Haitian patients<sup>38</sup>. 25 (6%) of the patients were switched to NVP because of CNS symptoms while 15 (3%) were switched to NVP due to gynaecomastia. Rash, nausea, and hepatitis were much less common; each occurring in less than 1% of the EFV treated cohort.

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<sup>32</sup> de Beaudrap P, Etard JF, Guèye FN, Guèye M, Landman R, Girard PM, et al. Long-term efficacy and tolerance of efavirenz- and nevirapine-containing regimens in adult HIV type 1 Senegalese patients. *AIDS Res Hum Retroviruses*. 2008 Jun;24(6):753-60.

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<sup>34</sup> Tanon AK, Eholié SP, Polneau S, Kra O, Elio F, Ehui E, et al. Efavirenz versus indinavir chez les patients naïfs infectés par le VIH-1 à Abidjan (Côte d'Ivoire). *Med Mal Infect*. 2008 May;38(5):264-9.

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## General safety studies from high income countries

The safety and tolerance of EFV was prospectively evaluated in 1033 Spanish patients for three months after initiating cART<sup>39</sup>. Adverse events affected 303 (29.3%) of patients, interrupting treatment in 85 patients (8.23%). EFV-induced cutaneous rash had an incidence of 5.9% ceasing treatment in 2.4% of patients while gastrointestinal disturbances had an incidence of 1.45% and elevation of liver function tests had an incidence of 0.68%. Cutaneous rash was more frequent among women (9.6% vs. 4.6%,  $p=0.004$ ). CNS events affected 249 participants (18.5%), resulting in 62 discontinuations (6% of all patients). The most frequent complaints for a total of 280 reported were dizziness (128 cases, 45.7%), sleep disorders (119 cases, 42.5%), mood disorders (27 cases, 9.7%), motor disorders (3 cases, 1.1%), and psychosis or delirium (3 cases, 1.1%). The median number of days from the start of efavirenz to onset of a CNS AE was 4 (IQR 1–14), and the median number of days until resolution in those who continued treatment was 9.5 (IQR 4–33). When treatment was interrupted, it was interrupted after a median of 4.5 days (IQR 0–12).

EFV and NVP based cART was prospectively compared in 67 Spanish patients<sup>40</sup>. Patients were randomised to regimens of d4T/ddI/EFV ( $n=29$ ) or d4T/ddI/NVP ( $n=35$ ). Four patients on EFV based therapy discontinued due to CNS symptoms (i.e. light-headedness, insomnia, and/or restlessness). 3 (10%) of patients on EFV developed a rash, 12 (41%) of patients reported CNS symptoms, 3 (10%) developed peripheral neuropathy, 13 (10%) reported GI symptoms, 5 (17%) developed lipodystrophy, 1 (3%) developed gynaecomastia, 2 (7%) had grade 1-2 liver enzyme elevation, 3 (10%) had grade 3-4 liver enzyme elevation, 5 (17%) developed hypercholesterolemia ( $>300$  mg/dL), and 1 (3%) developed hypertriglyceridaemia ( $>750$  mg/dL).

ddI/FTC/EFV was prospectively studied in 40 ARV naïve French patients over 24 weeks<sup>41</sup>. 73% of patients experienced mild-moderate CNS symptoms. CNS symptoms were defined as sleep disturbances with insomnia and abnormal dreaming, depression and mood changes, dizziness, or asthenia and lasted for a median of 28, 35, 4, and 34 days, respectively. 10% of patients experienced a maculopapular rash that cleared without treatment interruption. Discontinuation of the regimen due to toxicity occurred in one patient, who experienced gastrointestinal intolerance from ddI.

The efficacy and tolerability of long term AZT/3TC/EFV was prospectively evaluated in 422 American patients<sup>42</sup>. 14 (3%) developed hypercholesterolemia, 15 (4%) had elevations in ALT, 22 (5%) reported depression, 22 (5%) reported impaired

concentrations, 27 (7%) reported insomnia, 29 (7%) developed hypertriglyceridemia, 37 (9%) developed a maculopapular rash, and 36 (9%) developed dizziness. Psychiatric symptoms (aggressive reaction, suicide attempt, manic reaction, paranoid reaction, psychosis, or grade 3 or 4 depression) were reported in 8% of the patients. Grade 3 or 4 depression occurred in 4% of patients.

The metabolic profiles of NVP and EFV were analysed in a cross sectional study with 686 Italian patients<sup>43</sup>. 324 patients started on EFV while 299 initiated NVP. Patients were compared after 6 to  $\geq$  24 months of therapy. Triglyceridaemia, cholesterolaemia, and hyperglycaemia were defined by levels greater than 172, 230, and 110 mg/dL, respectively. Isolated triglyceridaemia was more common in ARV naïve patients on EFV based regimens ( $p=0.0027$ ). Combined triglyceridaemia and cholesterolaemia was also more common in patients on EFV ( $p < 0.0001$ ). Comparing all patients on EFV with all patients on NVP the frequency of elevated triglyceride, cholesterol, and glucose levels was much higher in those given EFV vs. NVP (160 vs. 71  $p<0.0001$ , 48 vs. 19  $p<0.0001$ , and 50 vs. 19  $p=0.0003$ , respectively). Gynaecomastia occurred in 13 patients on EFV and two on NVP ( $p=0.0074$ ). Lipodystrophy attributed to previous antiretroviral therapy improved in 25 patients on NVP compared to seven patients on EFV ( $p=0.0005$ ).

The safety and efficacy of TDF/3TC/EFV was prospectively evaluated in 154 Spanish patients<sup>44</sup>. After twelve months of therapy mean triglyceride levels dropped from 233 to 170 mg/dL ( $p < .01$ ) and the mean cholesterol levels decreased from 205 to 189 mg/dL ( $p < .01$ ). Nine patients reported EFV-induced CNS symptoms, seven of which discontinued due to the severity of the symptoms. One patient discontinued due to an EFV-induced rash.

An English cohort of 443 patients (96 female, 337 male) were included in a retrospective evaluation of EFV based cART<sup>45</sup>. 60 women and 161 men discontinued EFV. 48.4% of males discontinued due to CNS symptoms compared to 30% of females. Overall, 38.8% of women discontinued by week 48 compared to 28.3% of men. Eight men and three women discontinued due to rash.

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<sup>41</sup> Molina JM, Ferchal F, Rancinan C, Raffi F, Rozenbaum W, Sereni D, et al. Once-daily combination therapy with emtricitabine, didanosine, and efavirenz in human immunodeficiency virus-infected patients. *J Infect Dis*. 2000 Aug;182(2):599-602.

<sup>42</sup> Tashima K, Staszewski S, Nelson M, Rachlis A, Skiest D, Stryker R, et al. Efficacy and tolerability of long-term efavirenz plus nucleoside reverse transcriptase inhibitors for HIV-1 infection. *AIDS*. 2008 Jan 11;22(2):275-9.

<sup>43</sup> Manfredi R, Calza L, Chiodo F. An extremely different dysmetabolic profile between the two available nonnucleoside reverse transcriptase inhibitors: efavirenz and nevirapine. *J Acquir Immune Defic Syndr*. 2005 Feb 1;38(2):236-8.

<sup>44</sup> Arrizabalaga J, Arazo P, Aguirrebengoa K, García-Palomo D, Chocarro A, Labarga P, et al. Effectiveness and safety of simplification therapy with once-daily tenofovir, lamivudine, and efavirenz in

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HIV-1-infected patients with undetectable plasma viral load on HAART. HIV Clin Trials. 2007 Sep-Oct;8(5):328-36.

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## **Efavirenz Pharmacokinetics**

### ***Relationship between EFV concentrations and toxicity***

The role of EFV plasma concentrations in predicting CNS toxicity was evaluated in 130 Swiss patients <sup>46</sup>. Concentrations were drawn 12 hours after dose administration. Virological failure was seen in 50% of patients with an EFV concentration < 1000 ug/L versus 22 and 18% of patients with EFV concentrations between 1000-4000 ug/L and > 4000 ug/L, respectively. CNS toxicity (insomnia, dizziness, headache, fatigue) was 2.67 times more common in patients with EFV concentrations > 4000 ug/L compared with patients with concentrations between 1000-4000 ug/L.

A retrospective analysis of 843 Dutch patients evaluated the relationship between EFV plasma concentrations and discontinuations due to toxicity <sup>47</sup>. 138 patients discontinued due to toxicity, or by choice of the physician, while 705 patients continued EFV. 14.5% of patients who discontinued had a plasma concentration > 4mg/L compared to 14% of the patients who continued EFV (p=0.890). HCV infection was a predictor of EFV discontinuation in this analysis (p=0.026).

The above analysis supports a previous retrospective analysis of the 2NN trial which did not find any associations between NVP and EFV concentrations and adverse events <sup>48</sup>. However, patients with EFV concentrations > 2.18 mg/L were 4.4 times more likely to have elevated liver enzymes and the occurrence of elevated liver enzymes during the first six weeks of EFV therapy was significantly (p = 0.036) correlated to the EFV exposure (Cmin).

### ***Role of CYP2B6 genotype and increased EFV concentrations***

Relationships between the CYP2B6 G516T polymorphism and EFV plasma concentrations were evaluated in 152 patients <sup>49</sup>. Median EFV half-lives were 23, 27, and 48 hours for patients with CYP2B6 position 516 GG (78 patients), GT (60), and TT (14) genotypes, respectively (p<0.001). After therapy was stopped, plasma EFV concentrations in patients with GG, GT, and TT genotypes were predicted to exceed the estimated 95% inhibitory concentration for wild-type virus (46.7 ng/mL) for a median of 5.8 days (IQR, 4.4–8.3 days), 7.0 days (IQR, 5.0–8.0 days), and 14 days (IQR, 11.1–21.2 days), respectively (p<0.001). This is important to consider when discontinuing EFV based cART as NRTIs have shorter half lives, and if all three medications are discontinued at the same time EFV would be left to combat HIV on its own, increasing the risk for selecting NNRTI resistant HIV.

A pharmacokinetic study in Germany analysed the impact of CYP 2B6 polymorphisms on EFV and NVP plasma concentrations <sup>50</sup>. 225 Europeans and 146 Africans participated.

EFV and NVP concentrations were significantly associated with T983C ( $p < 0.0001$  and  $p=0.02$ , respectively) and G516T ( $p < 0.0001$  and  $p=0.002$ , respectively). BMI was related to EFV concentrations ( $p=0.04$ ) and age was related to NVP concentrations ( $p=0.05$ ).

The impact of different CYP2B6 alleles on EFV concentrations were evaluated in 169 American patients<sup>51</sup>. Two new loss-of-function alleles were found: allele \*27 (marked by 593T>C [M198T]), that results in 85% decrease in enzyme activity and allele \*28 (marked by 1132C>T), that results in protein truncation at arginine 378. Median AUC levels were 188.5 ug h/mL for individuals homozygous for a loss/diminished-function allele, 58.6 ug h/ml for carriers, and 43.7 ug h/mL for noncarriers ( $P<0.0001$ ). Patients with a poor metaboliser genotype had a likelihood of 35 of presenting with very high EFV plasma levels.

The impact of CYP2B6 G516T (\*6) genotype on EFV plasma concentrations was evaluated in 71 Zimbabwean patients<sup>52</sup>. Out of 71 genotyped patients, 49% had the CYP2B6\*6 allele variant, of whom 30%, 44%, and 27% were classified as extensive (G516G), intermediate (G516T), and poor (T516T) metabolizers of EFV, respectively. 50% of the patients had EFV concentrations  $> 4$  mg/L. Poor metabolizers and women patients tended to have higher EFV plasma concentrations. Pharmacokinetic analysis revealed that dose reduction to 400mg daily in poor metabolizing patients would maintain EFV concentrations in its therapeutic range.

CYP2B6 G516T's impact on NVP concentrations was studied in 23 Ugandan patients<sup>53</sup>. The median nevirapine trough concentration in individuals homozygous for the variant allele (TT) was 7607 ng/mL. In patients with the GG and GT alleles concentrations were 4181 and 5559 ng/mL, respectively (GG vs TT median ratio = 1.82;  $P=0.011$ ).

The relationship between EFV plasma concentrations, CNS toxicity, and CYP2B6 polymorphisms was evaluated in 89 American patients<sup>54</sup>. The CYP2B6 T516T genotype was more common in African Americans (20%) compared to European Americans (3%), and was associated with greater levels of EFV in the plasma ( $p<0.0001$ ). The CYP2B6 G516T genotype was associated with CNS symptoms at week one ( $p=0.036$ ) but not at week 24 ( $p=0.76$ ). The median EFV AUC was 44 ( $n=78$ ), 60 ( $n=60$ ), and 130 ( $n=14$ ) ug h/mL for the G/G, G/T, and T/T genotypes, respectively.

The impact of CYP2B6 polymorphisms on EFV concentrations and CNS toxicity was evaluated in 59 Swiss patients<sup>55</sup>. T516T was associated with greater plasma and intracellular concentrations with EFV, and greater plasma concentrations with NVP. Sleep disorders, mood disorders, and fatigue were not significantly associated with geometric mean plasma AUC. Geometric intracellular AUC was closely associated with mood disorders ( $p=0.01$ ) and fatigue ( $p=0.06$ ). Patients with CYP2B6 T516T were nearly more likely to have sleep disorders ( $p=0.06$ ), mood disorders ( $p=0.1$ ), and fatigue ( $p=0.08$ ) when compared to patients without this genotype.

The CYP2B6 G516T genotype was evaluated in 100 Spanish patients<sup>56</sup>. In this entirely Mediterranean population 52% had the wildtype homozygous GG, 43% had the heterozygous GT, and 5% had polymorphic homozygous TT genotype. Concentrations were higher in patients with at least one polymorphism in CYP2B6 compared to the wild type (2.65 mg/mL [IQR, 1.89–3.72 mg/mL] versus 1.71 mg/mL [IQR, 1.09–2.53 mg/mL];  $p < 0.01$ ). Concentrations were more likely to be subtherapeutic ( $< 1$  ug/mL) in patients with the wildtype versus the G516T genotype ( $p = 0.01$ ).

Summary: The data are conflicting regarding the relationship between high EFV concentrations and neurotoxicity. Evidence from Switzerland proves that there is a relationship between EFV troughs  $> 4000$  ug/L and neurotoxicity, but this doesn't appear to affect treatment discontinuations according to a Dutch study. CYP 2B6 genotype is affected by ethnic background. Some ethnicities are at a higher risk of achieving higher concentrations because of this diversity in genotype, and this may increase the risk of neurotoxicity in certain demographics. This increased risk must be recognized as EFV's role in the treatment of HIV in low and middle income countries increases.

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<sup>48</sup> Kappelhoff BS, van Leth F, Robinson PA, MacGregor TR, Baraldi E, Montella F, et al. Are adverse events of nevirapine and efavirenz related to plasma concentrations? *Antivir Ther*. 2005;10(4):489-98.

<sup>49</sup> Ribaldo HJ, Haas DW, Tierney C, Kim RB, Wilkinson GR, Gulick RM, et al. Pharmacogenetics of plasma efavirenz exposure after treatment discontinuation: an Adult AIDS Clinical Trials Group Study. *Clin Infect Dis*. 2006 Feb 1;42(3):401-7.

<sup>50</sup> Wyen C, Hendra H, Vogel M, Hoffmann C, Knechten H, Brockmeyer NH, et al. Impact of CYP2B6 983T>C polymorphism on non-nucleoside reverse transcriptase inhibitor plasma concentrations in HIV-infected patients. *J Antimicrob Chemother*. 2008 Apr;61(4):914-8.

<sup>51</sup> Rotger M, Tegude H, Colombo S, Cavassini M, Furrer H, Decosterd L, et al. Predictive value of known and novel alleles of CYP2B6 for efavirenz plasma concentrations in HIV-infected individuals. *Clin Pharmacol Ther*. 2007 Apr;81(4):557-66.

<sup>52</sup> Nyakutira C, Röshammar D, Chigutsa E, Chonzi P, Ashton M, Nhachi C, et al. High prevalence of the CYP2B6 516G-->T(\*6) variant and effect on the population pharmacokinetics of efavirenz in HIV/AIDS outpatients in Zimbabwe. *Eur J Clin Pharmacol*. 2008 Apr;64(4):357-65.

<sup>53</sup> Penzak SR, Kabuye G, Mugenyi P, Mbamanya F, Natarajan V, Alfaro RM, et al. Cytochrome P450 2B6 (CYP2B6) G516T influences nevirapine plasma concentrations in HIV-infected patients in Uganda. *HIV Med*. 2007 Mar;8(2):86-91.

<sup>54</sup> Haas DW, Ribaldo HJ, Kim RB, Tierney C, Wilkinson GR, Gulick RM, et al. Pharmacogenetics of efavirenz and central nervous system side effects: an Adult AIDS Clinical Trials Group study. *AIDS*. 2004 Dec 3;18(18):2391-400.

<sup>55</sup> Rotger M, Colombo S, Furrer H, Bleiber G, Buclin T, Lee BL, et al. Influence of CYP2B6 polymorphism on plasma and intracellular concentrations and toxicity of efavirenz and nevirapine in HIV-infected patients. *Pharmacogenet Genomics*. 2005 Jan;15(1):1-5.

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## Hypersensitivity reactions

There have been several case reports of EFV induced hypersensitivity. This typically presents as an erythematous maculopapular rash and acute hepatitis<sup>57 58 59</sup>. A French caucasian cohort found the HLA-DRB1\*01 to be significantly associated with cutaneous hypersensitivity induced by NVP or EFV in 21 patients<sup>60</sup>.

Two other case reports detailed EFV induced hypersensitivity, involving renal impairment<sup>61 62</sup>. In the report by Angel-Moreno-Maroto et al. the patient developed an acute hypersensitivity reaction to efavirenz with acute renal, hepatic, and pulmonary failure in the absence of rash and eosinophilia. While Curry et al. reported on a patient who developed acute interstitial nephritis. Another case report detailed pulmonary induced hypersensitivity by EFV<sup>63</sup>. This patient developed maculopapular pruritic rashes on the trunk and upper extremities, myalgia, a fever, and interstitial infiltration in both lungs.

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<sup>58</sup> Leung JM, O'Brien JG, Wong HK, Winslow DL. Efavirenz-induced hypersensitivity reaction manifesting in rash and hepatitis in a Latino male. *Ann Pharmacother*. 2008 Mar;42(3):425-9.

<sup>59</sup> Abrescia N, D'Abbraccio M, Figoni M, Busto A, Butrico E, De Marco M, et al. Fulminant hepatic failure after the start of an efavirenz-based HAART regimen in a treatment-naive female AIDS patient without hepatitis virus co-infection. *J Antimicrob Chemother*. 2002 Nov;50(5):763-5.

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<sup>61</sup> Curry E, Thomas M, Yehia M. Renal impairment and hypersensitivity reaction due to efavirenz. *Nephrology (Carlton)*. 2008 Dec;13(6):541.

<sup>62</sup> Angel-Moreno-Maroto A, Suárez-Castellano L, Hernández-Cabrera M, Pérez-Arellano JL. Severe efavirenz-induced hypersensitivity syndrome (not-DRESS) with acute renal failure. *J Infect*. 2006 Feb;52(2):e39-40.

<sup>63</sup> Behrens GM, Stoll M, Schmidt RE. Pulmonary hypersensitivity reaction induced by efavirenz. *Lancet*. 2001 May 12;357(9267):1503-4.

## Rash

There have been several cases of photosensitivity due to EFV<sup>64 65</sup>. A desensitization protocol for EFV induced rash was successfully implemented in a Canadian patient<sup>66</sup>. The protocol took 16 days to complete, with a day one dose of 0.5 mg which was gradually increased to a day 16 dose of 1200 mg.

A retrospective analysis in Thailand was unable to determine significant risk factors for recurrent rash with EFV in 122 patients who developed a rash with NVP<sup>67</sup>.

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<sup>65</sup> Yoshimoto E, Konishi M, Takahashi K, Murakawa K, Maeda K, Mikasa K, et al. The first case of efavirenz-induced photosensitivity in a Japanese patient with HIV infection. *Intern Med*. 2004 Jul;43(7):630-1.

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<sup>67</sup> Manosuthi W, Thongyen S, Chumpathat N, Muangchana K, Sungkanuparph S. Incidence and risk factors of rash associated with efavirenz in HIV-infected patients with preceding nevirapine-associated rash. *HIV Med.* 2006 Sep;7(6):378-82.

## Other adverse events

There have been several reports of EFV induced gynaecomastia<sup>68</sup>. All patients did have successful immunologic and virologic response to the therapy. Gynaecomastia occurred after 4-15 months, and was resolved after EFV withdrawal after a mean of five months.

A case report of EFV induced catatonia was reported in 2002<sup>69</sup>. This 47 year-old female patient had a history of depression, chronic low-grade suicidal ideation, and passive aggressive personality disorder. She developed catatonia, psychosis, and extreme psychomotor retardation. Her EFV concentration at catatonia diagnosis was 25,375 µg/mL, while concentrations of 1000-4000 µg/mL are generally recommended for maintaining efficacy and minimising toxicity<sup>70</sup>.

A case report of EFV induced haemolytic anaemia was reported in South Africa<sup>71</sup>. This 36 year-old female had the following lab values: Hgb 4.6 g/dL, MCV 88 fl, LDH 6570 U/L, haptoglobin < 0.2g/L, and polyspecific direct antibody test was positive. The patient was on d4T, 3TC, and EFV. The patient was switched to LPV/r and the anaemia resolved in two weeks, which is generally the time needed to clear EFV in patients without CYP 2B6 polymorphisms.

A case report of EFV induced torsade de pointes arrhythmia was reported in the United States<sup>72</sup>. When initiated on AZT/3TC/ABC/EFV this 63 year old African-American female developed syncope, while the EKG showed sinus tachycardia and marked QT prolongation. While on telemetry, the patient had multiple episodes of torsades. Once the therapy was switched to d4T/3TC/NFV the patient returned to normal sinus and rhythm.

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<sup>69</sup> Sabato S, Wesselingh S, Fuller A, Ray J, Mijch A. Efavirenz-induced catatonia. *AIDS.* 2002 Sep 6;16(13):1841-2.

<sup>70</sup> la Porte CJ, Back DJ, Blaschke T, Boucher CAB, Fletcher CV, Flexner C, et al. Updated guideline to perform therapeutic drug monitoring for antiretroviral agents. *Rev Antivir Ther.* 2006;3:4-14.

<sup>71</sup> Freercks RJ, Mehta U, Stead DF, Meintjes GA. Haemolytic anaemia associated with efavirenz. *AIDS.* 2006 May 12;20(8):1212-3.

<sup>72</sup> Castillo R, Pedalino RP, El-Sherif N, Turitto G. Efavirenz-associated QT prolongation and Torsade de Pointes arrhythmia. *Ann Pharmacother.* 2002 Jun;36(6):1006-8.

## Paediatrics

### ***Paediatric patients < 3 years of age***

The safety and efficacy of ddI/FTC/EFV was prospectively evaluated in 37 ARV naïve children<sup>73</sup>. The patients were split into three different cohorts based on age: 90 days-<3 years (group 1), 3-12 years (group 2 containing 21 patients), and 13-21 years (group 3 containing 16 patients). FTC was dosed 6mg/kg daily, ddI was dosed 240 mg/m<sup>2</sup> daily,

and EFV was dosed according to the package insert. There were two cases of adverse events causing treatment discontinuation, both due to a rash which developed in the first two weeks of therapy. Another patient had grade 3 dizziness during the first week on the regimen, which eventually subsided. The first group, consisting of six patients, was analysed separately and was recently presented<sup>74</sup>. EFV solution was dosed 390mg (<10kg) or 600 mg (>10kg). The median dose, half-life, CL/F, AUC, and C<sub>min</sub> for this group were 47 mg/kg, 11.4 hours, 14.4 L/h/m<sup>2</sup>, 66.2 mcg\*h/mL, and 1.1 mcg/mL.

BMS is currently enrolling patients for Study AI266-922 focusing on HIV paediatric patients aged 3 months to 6 years<sup>75</sup>. It will be assessing the safety, tolerability, and pharmacokinetics of ddI/FTC/EFV once daily. It will enrol approximately 32 patients. The primary outcome is assessing the pharmacokinetics of EFV derived from plasma concentrations versus time (up to 48 weeks). Secondary outcomes include efficacy (pVL < 50 cp/mL and 400 cp/mL measurements at weeks 24 and 48), adverse events, discontinuations due to adverse events, and laboratory abnormalities.

### **General safety studies**

A study in the Netherlands prospectively evaluated the efficacy and tolerability of EFV in 33 children (aged 2.1-16.7 years)<sup>76</sup>. The therapeutic range of EFV was defined as 1.0-4.0 mg/L. EFV was dosed according to information from the package insert. There were eight children who presented with persistent CNS symptoms. Five had difficulty concentrating, while sleep disorders, a psychotic reaction, and a seizure occurred in one child each. Six of these children discontinued therapy due to these adverse events. 27 children were able to tolerate EFV and all maintained a pVL < 50 cp/mL.

A retrospective analysis in Thailand assessed the efficacy and tolerability of NVP vs. EFV based cART in 139 children (aged 0.32 - 14.56 years)<sup>77</sup>. 78 patients were initiated on EFV based cART. EFV dosing was based on the package insert. Four of these children had sleep problems and nightmares, though they were able to tolerate EFV thereafter.

The safety and efficacy of the liquid formulation of EFV was prospectively evaluated in a cohort of 17 American children (aged 3.1-9.6 years)<sup>78</sup>. Adjusting for a 20% lower bioavailability of the liquid versus solid formulation of EFV the dosing was weight based (720mg\*(weight in kg/70)). Patients were on a combination of NRTIs, EFV, and NFV. One child developed grade 3 neutropenia at week 48. Eleven children (58%) developed a grade 2 toxicity. The most common were diarrhoea (6 children, 32%), neutropenia (6 children, 32%) and anaemia (2 children, 11%). One child developed Grade 2 skin rash that resolved without interruption of therapy.

A solid formulation of EFV in combination with NFV and NRTIs was prospectively evaluated in 57 children (aged 3.8-16.8 years)<sup>79</sup>. The most common treatment-related effects of at least moderate severity were: rash (30%), diarrhoea (18%), neutropenia (12%), and biochemical abnormalities (12%). 88% of rashes appeared within two weeks days after EFV initiation and lasted for a median of 6 days (range 2-37 days). Severe adverse effects included neutropenia in two children and hepatic toxicity, diarrhoea and

neutropenia, and rash with fever (temperature, >39°C) in one child each. Eight children had mild dizziness or lightheadedness that resolved once EFV was given at bedtime rather than in the morning.

The safety and efficacy of ABC/ddI/3TC/EFV was prospectively assessed in 36 children (median age 6.6, range 1.7-11.5 years)<sup>80</sup>. One patient discontinued therapy due to a grade 2 elevation in liver transaminase levels.

### ***Hypersensitivity reactions***

There was a case report of an EFV hypersensitivity reaction in a 6 year female treated with EFV/3TC/LPV/r<sup>81</sup>. The patient developed a diffuse, flat, erythematous, mildly pruritic rash ten days after this regimen was initiated. She subsequently developed fever, vomiting, diarrhoea, and abdominal pain. After all her antiretrovirals were discontinued the symptoms subsided. She was reinitiated on the same regimen with diphenhydramine and prednisone 1mg/kg every other day for two weeks. The evening after reinitiation she developed a fever again but this subsided the next day.

A nine year old patient in England developed acute liver failure with AZT/3TC/EFV<sup>82</sup>. Thirteen weeks after therapy was initiated the patient has an AST of 2753, an ALT of 793, a bilirubin of 138 umol/L, an INR of 1.5 (later reaching 4.17), and elevated IgE (which is common in drug induced toxic reactions). Hepatitis A, B, C, CMV, autoantibodies, and Epstein-Barr virus were negative. After two liver transplants the patient was prescribed AZT/3TC/RAL and though there is some fluctuation in his LFTs he appears to be well.

### ***HIV/TB coinfection***

The effect of rifampicin on EFV pharmacokinetics was prospectively evaluated in 15 HIV/TB coinfecting children (aged 3-15 years, weighing > 10kg)<sup>83</sup>. EFV concentrations were measured in 15 children during and after rifampicin based anti-TB therapy. EFV C<sub>min</sub> was not significantly different during vs. after anti-TB therapy (median 0.83 mg/L vs. 0.86 mg/L, p=0.125). During and after anti-TB treatment 9 (60%) and 8 (53%) of the children had subtherapeutic C<sub>min</sub> concentrations (<1 mg/L), respectively. EFV concentrations below 1 mg/L are likely to cause mutations creating HIV which is resistant to NNRTIs. Viral load results were available for 13 of the 15 children six months after initiating cART. The median C<sub>min</sub> among the 11 children with undetectable pVL (<50 cp/mL) was 1.47 mg/L. The other two children had pVL log values of 2.41 and 2.59, and had EFV C<sub>min</sub> concentrations of 0.30 mg/L and 0.60 mg/L.

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<sup>74</sup> Capparelli E, Rochon-Duck M, Robbins B, Rathore M, Birtto P, Hu C, et al. Age Related Pharmacokinetics (PK) of Efavirenz (EFV) Solution. 16th Conference on Retroviruses and Opportunistic Infections. Montreal, Canada, 8-11 February 2009 [Poster S-148].

<sup>75</sup> Safety, Tolerability and Pharmacokinetics of Efavirenz in HIV-Infected Children. Available at: <http://clinicaltrials.gov/ct2/show/NCT00364793>. Accessed 28 July 2009.

<sup>76</sup> Wintergerst U, Hoffmann F, Jansson A, Notheis G, Huss K, Kurowski M, et al. Antiviral efficacy, tolerability and pharmacokinetics of efavirenz in an unselected cohort of HIV-infected children. *J Antimicrob Chemother*. 2008 Jun;61(6):1336-9.

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- <sup>81</sup> Foti JL, Piatt JP. Hypersensitivity to efavirenz treated with corticosteroids in a 6-year-old child. *AIDS Patient Care STDS*. 2003 Jan;17(1):1-3.
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