reported in one study (Mankhatitham *et al.*, 2011) but not in others (Swaminathan *et al.*, 2011; Bonnet *et al.*, 2013).

Evidence for a relationship between hepatotoxicity and efavirenz blood levels is mixed. The pharmacokinetic substudy of the 2NN study, reported an association between higher plasma levels of efavirenz and liver enzyme elevations during the first 6 weeks of treatment (Kappelhoff *et al.*, 2005); an efavirenz level > 2180 ng/ml was associated with a 4.4-fold risk of elevated liver enzymes. Yimer *et al.* (2012) also reported a modest, but statistically significant, difference in plasma efavirenz levels between those with (1860 ng/ml) and those without (1170 ng/ml) hepatotoxicity in a prospective study of 285 Ethiopian patients. In a study of Cambodian HIV–TB co-infected patients, hepatoxicity was associated with a plasma level > 4000 ng/ml (Borand *et al.*, 2014). In contrast, in another study of 64 HIV-infected patients, efavirenz levels did not differ between those with and without underlying liver disease, and neither the frequency nor severity of liver function test abnormalities could be correlated with plasma efavirenz levels (Katsounas *et al.*, 2007).

6d. Fetal toxicity

Initial evidence suggested that efavirenz was teratogenic, specifically causing neural tube defects, and this led to recommendations in previous versions of treatment guidelines that its use should be avoided in pregnant women. However, accumulated clinical experience has indicated that the risk of teratogenicity is very low, if it exists at all, and most treatment guidelines no longer advise against efavirenz use in pregnant women, or in women who may become pregnant.

Initial concerns about teratogenicity were based on animal studies and human case reports. In a study of pregnant cynomolgus monkeys treated with efavirenz at a dose that produces plasma drug levels similar to those in humans given efavirenz 600 mg once daily, malformations were observed in 3 of 20 fetuses/infants from efavirenz-treated monkeys compared with none of 20 concomitant controls. The abnormalities observed were anencephaly and unilateral anophthalmia in one fetus, microphthalmia in another fetus, and cleft palate in the third fetus (Bristol-Myers Squibb, 2015). There are five case reports of neural tube defects and one case report of another central nervous system defect (Dandy-Walker syndrome) in infants from pregnant women who took efavirenz during pregnancy, all of whom were exposed in the first trimester. Of the four neural tube defects for which information is available, myelomeningocele was observed in two infants (De Santis *et al.*, 2002; Fundaro *et al.*, 2002; Saitoh *et al.*, 2005), anophthalmia with severe oblique facial clefts and amniotic banding in one infant (Shanske, 2012), and encephalocele in one infant (Gudu and Bekele, 2013).

The Antiretroviral Pregnancy Registry (APR), established by US public health agencies and physicians and sponsored by industry, receives and analyzes voluntary reports from clinicians of women exposed to antiretroviral agents during pregnancy and pregnancy outcomes. The January 2015 report of prospectively followed cases described 852 live births in women exposed to efavirenz in the first trimester. Birth defects were observed in 20 infants, including single cases of myelomeningocele and anophthalmia. The number of first-trimester exposures to efavirenz is sufficient to detect at least a twofold increase in risk in overall birth defects, and no such increase has been observed. Among women exposed to efavirenz in all trimesters, neither the overall frequency nor the nature of developmental abnormalities was outside the range expected in unexposed pregnancies (Antiretroviral Pregnancy Registry Steering Committee, 2015).

The risk of developmental abnormalities with first-trimester exposure to efavirenz has also been examined in several cohort studies. In ACTG protocols 219 and 219C, the rate of all congenital defects with efavirenz was 15.6% (Brogly *et al.*, 2010), but only 32 efavirenz-exposed infants were included, compared with the corresponding APR figure of 852 infants. A rate of 12.8% was reported in the ACTG P1025 study, but again numbers were low: only 47 efavirenz-exposed infants (Knapp *et al.*, 2012). In a study from the French Perinatal Cohort, the overall risk of birth defects in 372 infants with first-trimester efavirenz exposure was not increased; however, by organ system, 1.1% of exposed versus 0.4% of unexposed infants were born with neurological birth defects, a statistically significant association by one classification of birth defects but not by another (Sibiude *et al.*, 2014).

Other studies have provided reassuring data about the lack of fetal toxicity with efavirenz. Neural tube defects or an excess of other developmental abnormalities associated with first-trimester efavirenz exposure was not reported in two small case series from France (12 infants) and Botswana (22 infants) (Jeantils *et al.*, 2006; Bussmann *et al.*, 2007), in 205 infants in the National Study of HIV in Pregnancy and Childhood cohort from the UK and Ireland (Townsend *et al.*, 2009), and in 184 infants in a South African hospital cohort (Bera *et al.*, 2010). In serial meta-analyses between 2010 and 2014, there was no evidence of an increased risk of developmental abnormalities associated with first-trimester efavirenz exposure and only one case of a neural tube defect (Ford *et al.*, 2010; Ford *et al.*, 2011; Ford *et al.*, 2014).

Efavirenz is now recommended as first-line antiretroviral therapy in WHO guidelines regardless of pregnancy status or possibility of pregnancy in the future (World Health Organization, 2013; Siberry and Tindyebwa, 2014; World Health Organization, 2014). However, 2015 US guidelines still advocate caution (Panel on Antiretroviral Guidelines for Adults and Adolescents, 2015; Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission, 2015), advising that efavirenz does not need to be ceased in women who become pregnant while taking it (because most neural tube development has already taken place by the time pregnancy becomes apparent), but that women should not start treatment with efavirenz if they are of child-bearing age and are planning to or may become