CASE REPORT
Maternal deaths following nevirapine-based antiretroviral therapy

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We report 2 cases illustrating that it is too simplistic to link nevirapine (NVP) toxicity exclusively to individuals with immune preservation. Not enough is known about the mechanism of hepatotoxicity or cutaneous eruption to predict these events. This type of hypersensitivity reaction occurs rarely among HIV-exposed infants taking NVP prophylaxis or antiretroviral therapy (ART)-experienced adults with complete plasma viral load suppression. Conversely, HIV-uninfected adults and ART-naive pregnant women appear to be disproportionately affected by the adverse effects of NVP.

Over the last decade, South Africa (SA) has made major progress in the prevention of mother-to-child transmission (PMTCT) of HIV. PMTCT uptake among women known to be HIV-infected increased from 65% in 2006 to >90% in 2010,[1,2] and the most recent national mother-to-child transmission rate at 6 weeks postpartum (2.7%) is the lowest recorded to date.[1]

At the same time, maternal mortality-related HIV has continued to increase despite the increasing availability of antiretroviral therapy (ART). Data from the National Confidential Enquiry into Maternal Deaths show that 28% of all maternal deaths in 2008 - 2010 were AIDS-related, compared with an estimated 20% in 2002 - 2004.[3] The most recent report included a new category of maternal deaths, attributed to ART-related toxicity. The majority of the 73 deaths in this category were attributed to acute liver failure and Stevens-Johnson Syndrome (SJS). Although relatively uncommon, the occurrence of ART-related toxicity deaths was twice as high during 2010 than in previous years. This increase coincided with the release of the 2010 SA PMTCT guidelines[4] that promoted nevirapine (NVP)-based ART for pregnant women with World Health Organization (WHO) clinical stage 3 or 4 disease, regardless of CD4 cell count, hepatitis B infection, the presence of abnormal liver transaminases, or the need for tuberculosis co-treatment.

Recently, WHO noted its support for the expanded use of efavirenz (EFV) in pregnancy, based on growing evidence for the lack of EFV teratogenicity in the first trimester.[5] Still, many health professionals remain at odds over the choice of non-nucleoside reverse transcriptase inhibitors (NNRTIs) – EFV and NVP – particularly for pregnant women in the case of advanced immune suppression or during the first trimester.

Case reports are of limited value to the practice of evidence-based medicine, but they can illustrate the potential effect of clinical decisions. Previous recommendations to avoid EFV use in pregnancy were based largely on 5 case reports of birth defects in humans, 3 of which (myelomeningocele) resembled those from animal studies.[6] A recent case report of cleft palate and micropthalmia following EFV use at conception[7] is likely to re-ignite the debate around the safety and wider use of the drug in pregnancy. Although the handful of cases of birth defects that may be associated with EFV use are widely discussed, much less attention has been given to reports of much more common toxicities associated with NVP use. We report 2 recent cases of maternal deaths at our institution, both from liver failure, following initiation of NVP-based ART.

Case 1

A 22-year-old HIV-infected woman in her second pregnancy was commenced on tenofovir (TDF), lamivudine (3TC) and NVP at 31 weeks' gestation. Her nadir CD4 cell count was 201 cells/µl and alanine transaminase (ALT) was 14 IU/l at baseline. She was assessed as WHO clinical stage 1. After 2 weeks, the dose of NVP was doubled to 200 mg 12-hourly. Apart from haematinics, she received no other medication. Six weeks following ART initiation, she presented in labour with restlessness, jaundice, confusion, and an intra-uterine fetal death. Her alanine transaminase (ALT) was 462 IU/l, aspartate transaminase (AST) 134 IU/l and international normalised ratio (INR) >10. She delivered a fresh stillborn weighing 2.7 kg. She bled profusely following delivery, during which time she experienced a convulsion. The patient's capillary glucose was 2.4 mmol/l. Although she was adequately resuscitated and scheduled for exploration under anaesthesia, she had a cardiorespiratory arrest *en route* to theatre. She was declared dead after an hour of resuscitation. The woman's family declined a postmortem examination.

Case 2

A 29-year-old woman with nadir CD4 count 119 cells/µl was commenced on TDF, 3TC and NVP (initially 200 mg daily) at a peripheral clinic. She was 26 weeks pregnant. No baseline ALT measurement was performed and no other medication was prescribed. The patient presented a month later with a generalised rash and fulminant liver failure. By the time of referral to our facility, she was jaundiced, hypotensive, breathless, oliguric and had an altered level of consciousness. Her haemoglobin was 9.2 g/dl, white cell count 32.9 x 10^9/l, platelets 207 x 10^9/l, urea 8.8 mmol/l, creatinine 202 µmol/l, AST 548 IU/l and INR 4.47. Results of screening for malaria and viral hepatitis were negative. The patient was ventilated and received inotropic support. Ultrasound examination confirmed an *in utero* fetal death. A computed tomography scan of her brain was normal. She delivered a fresh stillborn after induction of labour. Postpartum, she developed grade 4 hepatic encephalopathy, persistent hypotension non-responsive to inotropic support, and worsening liver dysfunction (AST 568 IU/l, ALT 412 IU/l and INR 5.53), and required continued ventilation. The patient demised the following day.

Discussion

These cases are typical of the maternal deaths due to ART-related toxicity that are occurring with increasing frequency across SA. While the cases are not definitive and key investigations of interest (e.g. liver biopsy) are lacking, they provide a useful counterpoint to the case reports regarding EFV teratogenicity that have had a strong influence on SA policy.

Not enough is known about the mechanism of hepatotoxicity or cutaneous eruption related to NNRTIs to enable a reliable prediction of these events in people taking NVP. This type of hypersensitivity reaction occurs rarely among HIV-exposed infants taking NVP prophylaxis, or ART-experienced adults with complete plasma viral load suppression.[8] Conversely, HIV-uninfected adults and ART-naive pregnant women appear to be disproportionately affected by the adverse effects of NVP.[9] Severe adverse events following NVP-based ART among pregnant women are relatively common. In a cohort of pregnant women from Kenya, severe hepatotoxicity and severe rash occurred in 8% and 6%, respectively.[10]

Although the pharmacogenetic basis of NVP hypersensitivity is not well understood, there is some support for *HLA-DRB*1* allele and HLA-Cw8 expression in its pathogenesis.[11,12] A group of investigators recently identified NVP-derived adducts (haptens) with the *N*-terminal valine of haemoglobin, in 12/13 individuals receiving NVP-based ART.[13] Drug bio-activation to reactive metabolites, capable of forming protein adducts and binding to self-proteins, is believed to be the trigger behind these idiosyncratic allergic reactions. The detection of this adduct may provide a clue to the molecular mechanisms underlying NVP hypersensitivity.

The current British HIV Association Guidelines recommend either EFV- or NVP-based ART for pregnant women with a CD4 count <250 cells/µl.[14] The SA National Confidential Enquiry into Maternal Deaths has recommended EFV to replace NVP when initiating ART in pregnancy from the second trimester onwards.[3] Although a Cochrane review suggested the equivalence of EFV and NVP for efficacy endpoints in the treatment of HIV disease, EFV may be safer, notably for the development of raised liver transaminases and neutropenia.[15] Given that the United States Food and Drug Administration assigned EFV to pregnancy category D (indicating evidence of human fetal risk), it is unsurprising that there are no trials comparing NVP and EFV in pregnant women.[6] However, in the absence of head-to-head data on the choice of NNRTI in pregnancy, decision-making on the basis of case reports and series has led to conclusions that may not be in the best interests of the public's health.

Our view is that EFV should be recommended to all pregnant women in need of ART for their own health. Apart from regimen simplicity across all CD4 cell counts, there are a number of conditions unique to pregnancy (including pre-eclampsia; the haemolysis, elevated liver enzymes and low platelet (HELLP) syndrome; and acute fatty liver) that may mimic NVP toxicity, leading to inappropriate withdrawal of ART. Conversely, these conditions may delay diagnosis of NVP toxicity, with progression to overt liver failure. Although the evidence for EFV teratogenicity is equivocal, given the labelling of EFV, ART should be delayed until around 12 weeks' gestation to enable neural tube closure and embryogenesis of the face to be completed.[16]

Generally, there is a clear and urgent need for more evidence to inform the choice of NNRTI during pregnancy. We support calls for the development of a register of ART exposure during pregnancy, with particular focus on the first trimester. Given that the background prevalence of neural tube defects in some regions of SA is as high as 3.55/1 000 live births,[17] approximately 3 000 - 4 000 first-trimester EFV exposures would be required to identify (or rule out) the teratogenicity of EFV with some confidence. Until more useful data are available on the safety of EFV use around conception, the drug's use in the first trimester will remain a vexing issue.

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