P.O. Box 38597, Pinelands, Cape Town, South Africa, 7430
Email: afa@afadm.co.za
Website: www.aidforaids.co.za

Tel: 0800 227 700 or +27 (0)21 466 1700
Fax: 0800 600 773 or +27 (0)21 466 1744

Healthcare Professional Newsletter

September 2017 – Issue 46

Severe efavirenz-induced ataxia and encephalopathy

Efavirenz commonly causes early neuropsychiatric adverse events like dizziness, vivid dreams, euphoria or dysphoria. Patients who are genetic slow metabolisers of efavirenz (about 20% of South Africans) experience more severe early neuropsychiatric effects.[1] Fortunately, tolerance to these early neuropsychiatric effects develops within a few weeks, even in patients who are genetic slow metabolisers of efavirenz.[1]

A case series of severe efavirenz-induced encephalopathy has recently been published.[2] Twenty women presented over a 21-month period to Tshepong hospital, Klerksdorp, with ataxia, but no nystagmus, and 11 had encephalopathy. The women had been on an efavirenz-based regimen for a median of two years. Twelve of the 20 women weighed <40 kg and should have been treated with 400 mg of efavirenz, but all were on efavirenz 600 mg daily. Their efavirenz plasma concentrations were all above the therapeutic range, and 15 had efavirenz concentrations above the upper limit of normal (20 mg/L) of the assay. The neurological features gradually resolved after withdrawing efavirenz, and recurred on rechallenge in two women.

It is almost certain that these 20 women were genetic slow metabolisers of efavirenz. Prolonged exposure to high concentrations of efavirenz resulted in the ataxia and encephalopathy. Efavirenz and especially its 8-hydroxyl metabolite display neurotoxicity in vitro.[3] A fatal case of encephalopathy with ataxia with vacuolar axonopathy of the brain was reported from Groote Schuur hospital, Cape Town.[4]

The incidence of this syndrome of efavirenz-induced ataxia and encephalopathy is unknown, but it is striking that 20 cases were seen in less than 2 years in Tshepong hospital. It is likely that many other cases have been missed. The clinical presentation of unexplained ataxia, with or without encephalopathy, in patients on efavirenz is characteristic. The key investigation is the plasma efavirenz assay – if the concentration is above the therapeutic range then efavirenz should be stopped. Resolution should occur over days to weeks. It is important to dose efavirenz appropriately in people weighing <40 kg.

References:

1. Haas DW, Ribaudo HJ, Kim RB, et al. Pharmacogenetics of efavirenz and central nervous system side effects: an Adult AIDS Clinical Trials Group study. AIDS 2004;18:2391-2400.
2. Variava E, Sigauke FR, Norman J, et al. Late efavirenz-induced ataxia and encephalopathy: a case series. JAIDS 2017;75:577-9.
3. Decloedt E, Maartens G. Neuronal toxicity of efavirenz: a systematic review. Expert Opin Drug Saf 2013;12:841–846.
4. Kenyon C, Mfolozi S, Croxford R, et al. Severe efavirenz-induced vacuolar axonopathy complicated by fatal aspiration pneumonia. Br J Clin Pharmacol 2012;74:1070–1072.

Contributors:
Prof. Gary Maartens
Prof. Mark Cotton
Prof. Graeme Meintjes

This newsletter has been edited by:
Liezl Dunn
Linda Doms

Prolonged post-treatment virologic control in a South African HIV+ child after early antiretroviral therapy – implications for the future?

The concept of initiating antiretrovirals during acute HIV infection was first studied between 1991 and 1994, when the high levels of viral replication was first recognised in this period. In a placebo-controlled randomised trial of adults with the acute retroviral syndrome, zidovudine monotherapy for 6 months was associated with a lower rate of disease progression.[1] More recently, the VISCONTI cohort (Viro-Immunologic Sustained Control After Treatment Interruption) comprising 14 adults with post treatment control was described.[2] All had initiated combination antiretroviral therapy (ART) in the late 90s and early 2000s during acute HIV infection, were treated for approximately 4 years, and had either undetectable or very low plasma HIV RNA levels for a median of 8 years after stopping ART.

Until recently, only 2 paediatric cases with post treatment control had been identified. The first was the Mississippi child, who received ART from 31 hours of age, interrupted ART after 18 months and spent almost 2 years with undetectable plasma HIV RNA, before relapsing.[3] The second, born in France, commenced ART at 3 months of age, stopped ART 5 to 6 years later, and has had undetectable plasma HIV RNA for approximately 11 years.[4]

In July 2017, a South African paediatric post treatment controller was described.[5] This child had participated in the Children with HIV early antiretroviral therapy (CHER) trial, which was a randomised trial comparing the standard of care at the time, delaying ART until CD4+ T-cell depletion or clinical progression begins, versus immediate ART for either 1 or 2 years followed by ART interruption. ART would be restarted according to subsequent CD4+ T-cell depletion or clinical progression.[6]

The child's plasma HIV RNA was >750,000 copies per ml at 6 weeks of age and 150,000 copies per ml when initiating ART at 8 weeks. Plasma HIV RNA, determined retrospectively, was below detectable limits after 40 weeks, when ART was discontinued as per protocol. After more than 8 years, the plasma HIV level remained undetectable but HIV DNA was present at very low levels in peripheral blood mononuclear cells. HIV antibodies were undetectable by standard enzyme-linked immuno-assay.[5]

What are the implications of this new paediatric case report? Post treatment control is a rare event, occurring in only one of more than 200 children stopping ART after early initiation. Both negative HIV antibody tests[7] and HIV DNA by PCR are often found a few years later after starting early suppressive ART.[8] However, virologic rebound is common after stopping ART.[8,9] While this case report offers hope for understanding mechanisms of HIV control, ART should not be discontinued outside of carefully monitored research studies. However, the first component, early initiation of continuous ART, is easily implementable and will both limit HIV reservoir size and preserve immune function. We hope that these children will benefit in the future from emerging understanding of immunological and genetic factors essential to control HIV replication.

References:

1. Kinloch-De Loes S, Hirschel BJ, Hoen B, Cooper DA, Tindall B, Carr A, et al. A controlled trial of zidovudine in primary human immunodeficiency virus infection. *N Engl J Med* 1995; 333(7):408-413.
2. Saez-Cirion A, Bacchus C, Hocqueloux L, Avettand-Fenoel V, Girault I, Lecuroux C, et al. Post-treatment HIV-1 controllers with a long-term virological remission after the interruption of early initiated antiretroviral therapy ANRS VISCONTI Study. *PLoS Pathog* 2013; 9(3):e1003211.
3. Luzuriaga K, Gay H, Ziemniak C, Sanborn KB, Somasundaran M, Rainwater-Lovett K, et al. Viremic relapse after HIV-1 remission in a perinatally infected child. *N Engl J Med* 2015; 372(8):786-788.
4. Frange P, Faye A, Avettand-Fenoel V, Bellaton E, Descamps D, Angin M, et al. HIV-1 virological remission lasting more than 12 years after interruption of early antiretroviral therapy in a perinatally infected teenager enrolled in the French ANRS EPF-CO10 paediatric cohort: a case report. *Lancet HIV* 2016; 3(1):e49-54.
5. Violari A, Cotton M, F., Kuhn L, Schramm DB, Paximadis M, Shalekoff S, et al. Viral and host characteristics of a child with perinatal HIV-1 following a prolonged period after ART cessation in the CHER trial. In: *IAS*. Paris; 2017.

6. Cotton MF, Violari A, Otwombe K, Panchia R, Dobbels E, Rabie H, et al. Early time-limited antiretroviral therapy versus deferred therapy in South African infants infected with HIV: results from the children with HIV early antiretroviral (CHER) randomised trial. *The Lancet* 2013; 382(9904):1555-1563.
7. Payne H, Mkhize N, Otwombe K, Lewis J, Panchia R, Callard R, et al. Reactivity of routine HIV antibody tests in children who initiated antiretroviral therapy in early infancy as part of the Children with HIV Early Antiretroviral Therapy (CHER) trial: a retrospective analysis. *Lancet Infect Dis* 2015.
8. Garcia-Prats AJ, Draper HR, Sanders JE, Agrawal AK, Mohapi EQ, Schutze GE. False negative post-18 month confirmatory HIV tests in HIV DNA PCR positive children: a retrospective analysis from Lesotho. *AIDS* 2012.
9. Butler KM, Gavin P, Coughlan S, Rochford A, Mc Donagh S, Cunningham O, et al. Rapid viral rebound after 4 years of suppressive therapy in a seronegative HIV-1 infected infant treated from birth. *Pediatr Infect Dis J* 2015; 34(3):e48-51.

The DAWNING trial: dolutegravir in second-line ART

At the 9th International AIDS Society Conference on HIV Science held in Paris in July 2017, interim results of the DAWNING trial were presented. This open-label randomised controlled trial compared a novel second-line ART regimen of dolutegravir plus 2 NRTIs versus lopinavir/ritonavir plus 2 NRTIs (the latter is a commonly used second-line regimen in South Africa and one which the WHO currently recommends). Participants were adult patients who had previously failed a first-line regimen of 2NRTIs plus an NNRTI. All participants had a resistance test performed at screening and were only eligible for the trial if they had at least one fully active NRTI – this is important in considering which patients these findings apply to.

Following an interim review, the Independent Data Monitoring Committee recommended discontinuation of the lopinavir/ritonavir arm because the virologic suppression results favoured the dolutegravir arm. Participants on lopinavir/ritonavir were then switched to dolutegravir.

A total of 624 participants were enrolled. At 24 weeks, by intention to treat 82% in the dolutegravir arm and 69% in the lopinavir/ritonavir arm had a viral load < 50 copies/ml, and statistical tests showed that dolutegravir was therefore superior to lopinavir/ritonavir (absolute difference in suppression = 13.8% in favour of dolutegravir, 95%CI = 7.3-20.3, P<0.001). The difference in virologic suppression was similar at week 48 for those participants who reached this time point. This difference was primarily driven by the higher rate of virologic failure in the lopinavir/ritonavir arm. There appeared to be more gastro-intestinal adverse events in the lopinavir/ritonavir arm, but the two arms were similar in terms of neuropsychiatric adverse events. No treatment emergent drug-resistance mutations were detected in the dolutegravir arm.

These findings suggest that, provided there is at least one fully active NRTI, then dolutegravir could be considered as the backbone of a second-line ART regimen after a patient has failed an NNRTI-containing first-line regimen. The presence of one fully active NRTI can be ascertained on resistance testing but can also be deduced from the sequence in which NRTIs are used. For example, if tenofovir/emtricitabine have been used as the only NRTIs in first line the mutations for which these two NRTIs select do not cause cross-resistance to zidovudine; therefore it can be assumed that zidovudine remains fully active. The reverse is not true for patients who have failed a first-line regimen containing zidovudine – this may cause cross-resistance to tenofovir.

AfA awaits the publication of the DAWNING findings in full before updating the guidelines.