

## Overdose with HAART – are we managing these patients adequately?

Tarryn Gabler, Bradley Yudelowitz, Adam Mahomed

**To the Editor:** Increasing numbers of HIV/AIDS-infected individuals have presented to medical casualty at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) after attempting suicide by overdosing on their antiretroviral therapy. Since 2009, medical gastro-enterology at CMJAH has been the primary specialty unit for cases of accidental or intentional overdose. Psychiatry and other medical sub-specialties are consulted as needed. Our unit sees approximately 1 case a month of accidental/intentional overdose with antiretrovirals. Between January and September 2010, 6% of all overdoses seen at CMJAH were of antiretroviral origin. Supportive care is provided and patients undergo psychiatric evaluation.

The information available on overdoses with antiretrovirals is from studies in developed countries, where intravenous drug users and men who have sex with men make up the bulk of the HIV-positive population. This differs significantly from South Africa, which now has the largest antiretroviral programme in the world. With little evidence related to this type of overdose, are we approaching the management, monitoring and follow-up of these patients correctly?

### Case report

A 42-year-old woman presented to the medical casualty department after taking 60 lamivudine (3TC) tablets and 60 stavudine (D4T) tablets for the purpose of deliberate self-harm. She had been on highly active antiretroviral therapy (HAART) for 2 years. Stressors leading to the suicide attempt included the diagnosis of HIV and side-effects of HAART.

Initial complaints included abdominal pain and nausea but no vomiting. Clinical examination and biochemical investigations (full blood count, urea and electrolytes, salicylate and paracetamol levels, liver function tests, lipase level and international normalised ratio) yielded no abnormalities. Blood gas measurement performed in casualty showed a normal pH and lactate level. Unfortunately drug level monitoring for the specific antiretrovirals ingested could not be performed, as this resource is not available at CMJAH.

The patient was treated with activated charcoal, approximately 2 hours after ingesting the HAART overdose; metaclopramide for nausea and vomiting and hyoscine butylbromide for abdominal cramps were administered intravenously. On admission a diagnosis of adjustment disorder with major depressive disorder and suicidality was made. Citalopram 40 mg daily was started and after 5 days she was discharged for follow-up in the psychiatric outpatient department. She was to continue receiving HAART from her local clinic.

Chris Hani Baragwanath Hospital and Hanyani HIV Clinic, Chiawelo, Soweto  
Tarryn Gabler, BSc Biomed Sci, MB BCH

Reproductive Health and HIV Research Unit, University of the Witwatersrand, Johannesburg  
Bradley Yudelowitz, MB BCH, Dip HIV Man (SA)

Division of Medical Gastroenterology, Department of Internal Medicine, Charlotte Maxeke Johannesburg Academic Hospital and University of the Witwatersrand  
Adam Mahomed, MB BCH, FCP (SA), Cert Gastro (SA)

Corresponding author: T Gabler (tarryn.gabler@hotmail.com)

This case identified many unanswered questions and prompted a review of the relevant literature. Ethics approval was obtained to review admission records from the University of the Witwatersrand Ethics Committee.

### Discussion

The literature search yielded few case reports describing accidental or intentional overdose on antiretroviral agents. Three of these concerned confusion between nevirapine and nelfinavir, where the opposite dosages were taken.<sup>1</sup> Two of these patients presented with severe fatigue, hypersomnia and nausea, and the third patient, a neonate who had accidentally been given an overdose of nevirapine, had asymptomatic neutropenia and hyperlactataemia.<sup>2</sup> In one case of an accidental overdose of ritonavir the patient experienced tiredness, headache, dry mouth, circumoral paraesthesiae, dizziness and disequilibrium of gait, and an electrocardiogram revealed a prolonged QT interval.<sup>3</sup> There is only 1 report of pharmacokinetic follow-up over 10 days after acute intoxication with nevirapine.<sup>4</sup> In all cases, symptomatic and supportive treatment was the only treatment necessary and all patients recovered fully.<sup>1-4</sup> In a review of 79 cases of indinavir overdose the authors concluded that side-effects of overdose, whether acute or chronic, were generally consistent with the safety profile of the drug.<sup>5</sup> Only one series of 4 case studies reported life-threatening side-effects and 1 death related to zidovudine overdose in neonates, where zidovudine-induced neutropenia led to opportunistic bacterial infections.<sup>6</sup>

Before the advent of HAART, AIDS-related deaths were the leading cause of death in HIV-positive patients. With the introduction of successfully implemented HAART in the USA, the number of AIDS-related deaths in HIV-infected individuals has decreased while the number of deaths due to non-AIDS-related diseases and malignancies has increased.<sup>7,8</sup> In Alberta, Canada, post-HAART, 32% of all deaths in HIV-positive patients are non-AIDS related (7% of these being due to suicide).<sup>9</sup> Other studies suggest that 10 - 30% of these suicides are due to overdose.<sup>10</sup>

As HIV is a chronic disease, it is not surprising that the increased rate of suicidal ideation and behaviour in HIV-positive individuals parallels that seen in other medically ill groups with life-threatening disorders.<sup>9,11</sup> Individuals with HIV/AIDS have an increased rate of suicidal ideation, suicide attempts and completed suicide.<sup>9</sup> Their risk factors for suicide include current stressors (e.g. unemployment, bereavement and stigmatisation), poor adaptive functioning, hopelessness, neuroticism and decreased social support.<sup>9</sup>

All these factors are thought to be due to the combination of increased susceptibility to mental illness as a result of HIV diagnosis and infection, opportunistic infection, socio-economic factors and neuropsychiatric side-effects of antiretrovirals. The latter may also be exacerbated when antiretrovirals interact with other drugs taken concurrently.<sup>12,13</sup>

Most previous case reports deal with accidental overdoses, in which doses are far lower than taken by people intending to harm themselves. Toxic effects of antiretrovirals in the acute setting are similar to their chronic side-effects, so patients who have overdosed deliberately can be expected to present with the same side-effects that would be expected after prolonged use.<sup>5,14</sup>

Management in our unit remains supportive with a biopsychosocial approach dealing with complications as and when they arise. Many unanswered remaining questions deserve further study.

- Should specific treatment be instituted, e.g. antidotes or the use of haemodialysis to aid the excretion of certain drugs, and is the use of activated charcoal beneficial?
- Does length of time on HAART before overdose influence the complication rate?
- Can drug level monitoring help confirm the diagnosis, estimate toxicity and estimate when HAART can be restarted after overdose, where the half-life of drugs taken in overdose can be prolonged compared with therapeutic dosing?<sup>10</sup>
- Do we risk causing a 'functional monotherapy' when stopping combinations of antiretrovirals with different half-lives at the same time, and will this lead to acquisition of new drug-related mutations?<sup>15</sup>
- Is our health care system, specifically mental health care, equipped to handle this new challenge?

#### References

1. Max B, Mourikes N. Confusion with nelfinavir and nevirapine. *N Engl J Med* 1998;338(6):396-397.
2. Brasme JF, Mille F, Benhayoun M, et al. Uncomplicated outcome after an accidental overdose of nevirapine in a newborn. *Eur J Pediatr* 2008;167(6):689-690.
3. Roberts DM, Ray JE, Buckley N. Mild clinical toxicity and dose-dependent pharmacokinetics following acute lopinavir/ritonavir poisoning in a HIV-positive patient. *AIDS* 2008;22(6):792-793.
4. Elens L, Haufroid V, Doyen C, Vandercam B, Yombi JC. Acute intoxication with nevirapine in an HIV-1-infected patient: clinical and pharmacokinetic follow up. *AIDS* 2009;23(10):1291-1293.
5. Lehman HP, Benson JO, Beninger PR, Anderson CA, Blumenthal SJ, Sharrar RG. A 5-year evaluation of reports of overdose with indinavir sulphate. *Pharmacoepidemiol Drug Saf* 2003;12(6):447-458.
6. Chiappiani E, Galli L, Gabiano C, et al. Preventable zidovudine overdose during postnatal prophylaxis in healthy children born to HIV-1 positive mothers. *AIDS* 2008;22:316-317.
7. Loui JK, Hsu LC, Osmond DH, Katz MH, Schwarcz SK. Trends in causes of death among persons with acquired immune deficiency syndrome in the era of highly active antiretroviral therapy, San Francisco 1994-1998. *J Infect Dis* 2002;186:1023-1027.
8. Sackoff JE, Hanna DB, Pfeiffer MR, Torien LV. Causes of death among persons with AIDS in the era of highly active antiretroviral therapy: New York City. *Ann Intern Med* 2006;145(6):397-406.
9. Krentz HB, Kliever G, Gill MJ. Changing mortality rates and causes of death for HIV infected individuals living in Alberta, Canada from 1984-2003. *HIV Med* 2005;6:99-106.
10. Roberts DM, Ray JE, Buckley NA. Mild clinical toxicity and dose dependant pharmacokinetics following acute lopinavir/ritonavir poisoning in an HIV positive patient. *AIDS* 2008;22:792-793.
11. Carrico AW, Johnson MO, Morin SF, et al. Correlates of suicidal ideation among HIV-positive persons. *AIDS* 2007;21(9):199-203.
12. Wynn GH, Cozza KL, Zapor MJ, Wortmann GW, Armstrong SC. Antiretrovirals part III: Antiretrovirals and drugs of abuse. *Psychosomatics* 2005;46:79-87.
13. Guarinieri M. Interaction of Drugs and Antiretrovirals. Newsletter of the Central and Eastern European Reduction of Harm Network 2003;5(1):9-10. <http://www.ahrn.net> (accessed 25 January 2011).
14. Olson K, Anderson IB, Benowitz NL, et al, eds. *Poisoning and Drug Overdose*. 4th ed. New York: McGraw Hill, 2004:111-115.
15. Tommasi C, Nicastrì E, Corpolongo A, et al. Stopping antiretroviral therapy: role for therapeutic drug monitoring. *AIDS* 2008;22(2):315-316.

*Accepted 31 May 2011.*