Correspondence

AIDS 2009, **23**:1291–1296

Acute intoxication with nevirapine in an HIV-1-infected patient: clinical and pharmacokinetic follow up

A 35-year-old homosexual man was diagnosed HIV-1 positive in July 2000, and HAART [nevirapine (NVP) 200 mg and epivir–azidothymidine (3TC–AZT) 150/250 mg twice daily (b.i.d.)] was immediately initiated, despite a sufficient CD4 cell count of 669 cells/μl on the basis of the viral load that was 66 000 copies/ml. After 3 months of treatment, his viral load was undetectable (<50 copies/ml). The rate of CD4 cells quickly raised over 1000 cells/μl after treatment initiation and remained over 800 cells/μl, thereafter. The levels of hepatic enzymes [glutamate oxaloacetate transaminase (GOT), glutamic pyruvate transaminase (GPT), gamma-glutamyl transferase (GGT) and alkaline phosphatase] were normal at the beginning of the treatment (Fig. 1a). The evolution of these enzymes after treatment initiation is reported in Fig. 1a and indicates that levels of GGT raised above normal levels and remained high up to date.

In November 2007, the patient was admitted to the emergency department for a suicidal attempt. He had ingested 30 pills of NVP 200 mg, 1.5 h before his hospitalization. The biology was not unusual with normal levels of GOT and GPT but somewhat elevated with GGT (131 IU/l) levels that was not surprising regarding his clinical history (Fig. 1a). Furthermore, no cutaneous manifestations were noticed. NVP treatment was discontinued between 27 November (day of intoxication) and 6 December when the NVP plasma concentrations were returned below the established efficacy threshold. During this period, the patient has taken the association of 3TC–AZT alone.

At each visit of the patient from the day of acute intoxication, samples were drawn on heparinized tubes for the pharmacokinetic analysis. Plasma drug concentrations of NVP were determined by a validated ultra performance liquid chromatography method with diode array detection (UPLC-DAD) [1]. In total, eight samples were obtained during the 10 days of follow-up. Kinetic results are shown in Table 1 and Fig. 1b.

HAART remains associated with a number of serious and potentially life-threatening adverse events, including drug-induced liver injury (so called 'hepatotoxicity') [2]. It is a common knowledge that the administration of nonnucleoside reverse transcriptase inhibitors (NNRTIs), especially NVP, is frequently associated with abnormal liver enzyme levels [3], and previous studies have associated several risk factors with NVP-induced hepatotoxicity [4]. Higher risk of elevated hepatic transaminases in antiretroviral-naive hepatitis C seronegative population receiving NVP-containing regimen has been related to sex and $CD4^+$ T-cell count. As our patient was a man with CD4 cell count more than 400 cells/μl, he was at risk to develop hepatotoxicity [5]. Consistently, the patient showed increased levels of GGT after treatment initiation.

Pharmacokinetics of NVP has been studied in the literature [6] but not yet, to the best of our knowledge, in case of acute intoxication. In the present study, the pharmacokinetic profile was established after a NVP intake of 6000 mg (30 pills of 200 mg). C_{max} was found to correspond to the first sampling time. However, in the literature, it is reported that T_{max} is around 2 h [6]. Therefore, the C_{max} reported here might be slightly underestimated as the first sampling time was 3 h after NVP intake. Whatever, C_{max} was approximately 4.5 times higher than in a 400 mg once daily regimen (30.6 versus 6.7 mg/l) and five times higher than in a 200 mg b.i.d. regimen (30.6 versus 5.9 mg/l) [6]. Total area under curve $(AUC)_{0-\infty}$ was approximately 17 times higher than previously reported for both once daily and b.i.d. regimens (1751.3 versus 101.8 and 109.0 h mg/l, respectively).

The calculated values for $T_{1/2}$ (30.1 h), Cl/F (3.4 l/h) and V/F were in agreement with previous findings [6,7], indicating that these pharmacokinetic parameters obtained in pharmacological situations remain valid in the case of acute intoxication. After 10 days of washing out, NVP was resumed when its plasmatic concentration was 0.15 mg/l.

A relationship between high plasma concentration and toxic response was demonstrated for efavirenz [8,9], but no conclusive association has been established between NVP plasma levels and hepatotoxicity [9–13]. Our results are in agreement with the conclusions of Dailly *et al.* [10] and de Maat *et al.* [11] who found no relationship between high NVP plasma concentrations and hepatotoxicity. Indeed, despite high NVP plasma levels, our patient showed stable transaminases compared with the levels observed prior to intoxication (Fig. 1a).

It has been clearly established that there is a risk of viral resistance emergence if all components of an NVP-based therapy are discontinued at the same time because of the prolonged elimination half-life of NVP compared with NRTIs. In that way, it has been found that continuation of the NRTI backbone for at least 5 days, allowing the

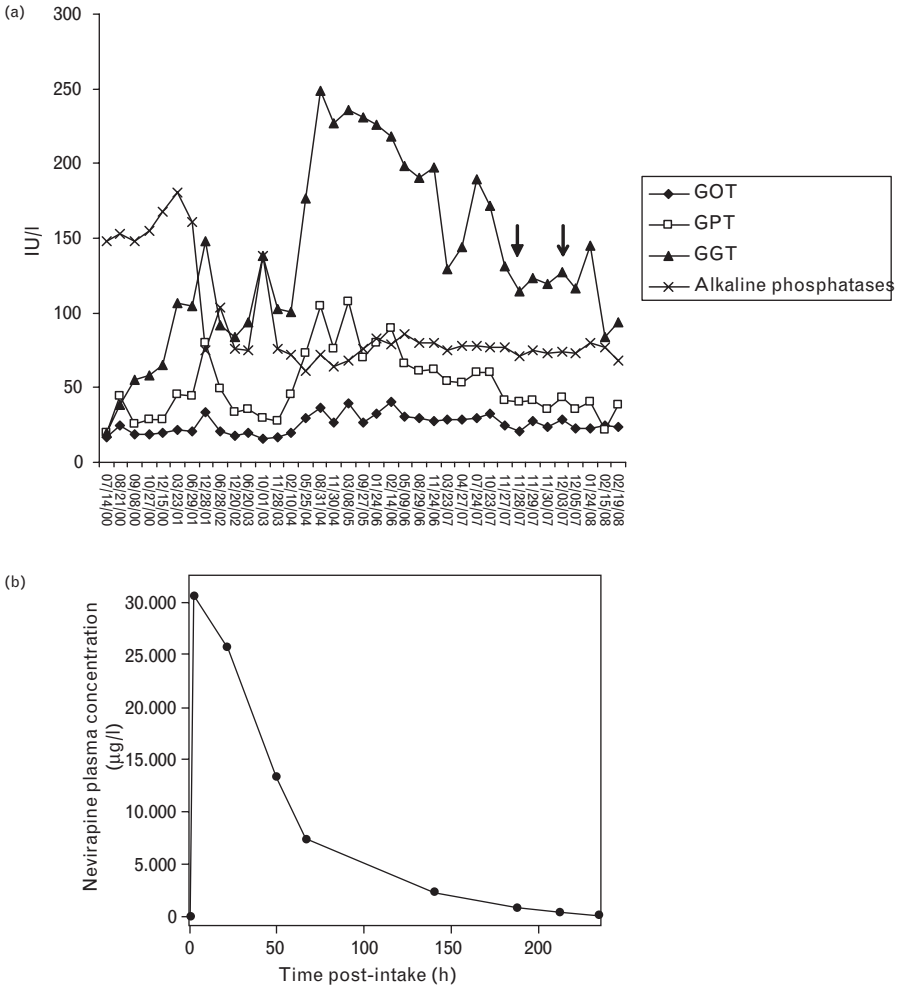

Fig. 1. Clinical and pharmacokinetic follow up. (a) Evolution of hepatic enzymes. Bold arrow indicates day of intoxication. Small arrow indicates day of treatment resumption. (b) Nevirapine plasma concentrations versus time curve. GGT, gamma-glutamyl transferase; GOT, glutamate oxaloacetate transaminase; GPT, glutamic pyruvate transaminase.

elimination of NVP below the zone of selective pressure (0.02–3.4 mg/l), may avoid the development of drug resistance in case of stopping classical NVP-based therapy in patients at steady state [14,15]. In case of NVP acute exposure, we have shown that even after 10 days, the patient had NVP concentrations above the threshold of the zone of selective pressure (0.02 mg/l). In this situation, it is clear that continuation of the dual NRTI regimen had to be applied when stopping NVP after intoxication. On the contrary, we have shown that $T_{1/2}$, Cl/F and V/F remain valid in the case of acute intoxication. Consequently, these parameters could also help the clinician to guide antiretroviral therapy (ART) management during episodes of acute NVP intoxication. In our patient, the NVP plasma levels returned to normal values after 10 days, so that the NVP-based therapy was resumed. The patient did not develop any virological treatment failure since this intoxication episode.

Table 1. Nevirapine pharmacokinetics parameters.

Parameter	Value
$AUC_{235\,h}$ (h mg/l)	1744.7
$AUC_{0\text{-}\infty}$ (h mg/l)	1751.3
C_{max} (mg/l)	30.6
T_{max} (h)	3
$T_{1/2}$ (h)	30.1
Cl/F (l/h)	3.4
Cl/F (l/h kg)	0.04
V/F (l)	148.8
V/F (l/kg)	1.9

AUC, area under curve.

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Received: 10 November 2008; accepted: 22 November 2008.

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DOI:10.1097/QAD.0b013e328325d61f

Etravirine plasma levels in a patient with decompensated liver disease

Case report

A 50-year-old African lady who was tested HIV positive in 1996 started antiretroviral therapy in 1998, and she was previously exposed to zidovudine, stavudine, didanosine (DDI), indinavir, saquinavir and nelfinavir.

Her HAART switches since 1998 were for side effects, drug toxicities and/or virologic failure/resistance. The last 4 years she had been on tenofovir (TDF), DDI and boosted fosamprenavir/r (fAMP/r). She had also been on minocycline for a year for acne.

In January 2008, she presented with abdominal distension and discomfort; clinically, she had ascites. Investigation revealed liver cirrhosis and portal vein thrombosis, normal liver function [alanine transaminase (ALT), aspartate transaminase (AST), platelet function, alpha fetoprotein, albumin and clotting time] and raised cancer antigen-125 (CA-125). She was anticoagulated; liver biopsy was deferred. The possibility of a drug-related cause was considered. We switched the regimen in a step-wise manner initially to TDF, DDI and etravirine (ETV) and then to TDF, ETV and boosted darunavir (DRV/r). Minocycline was also discontinued.

Further investigation revealed liver fibrosis/cirrhosis on biopsy, although the exact cause still remains unclear. She remains anticoagulated, and her decompensated cirrhosis is managed in collaboration with the hepatologists.

She remained stable and maintained her HIV viral load at below the level of detection.

ETV therapeutic drug monitoring (TDM) became available about 8 months into her new HAART regimen (TDF, ETV and DRV/r); ETV level was reported to be 3257 ng/ml, which is about 60 times the alleged target concentration on standard dosing [200 mg twice daily (b.i.d.)]. ETV was discontinued immediately. Serial ETV plasma concentration monitoring was performed at weeks 2 and 5 after discontinuation and were 931 and 100 ng/ml, that is, 18 times and twice the target level, respectively (Fig. 1). The half-life of ETV in this patient was estimated using the three data points (WinNonLin; Pharsight, Mountain View, California, USA) and was

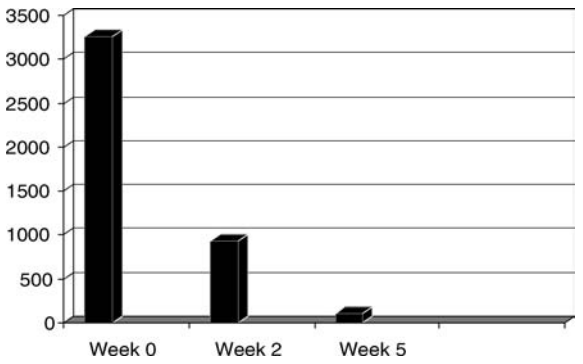

Fig. 1. Time in weeks from discontinuing etravirine; week 0, etravirine discontinued based on last etravirine plasma level on 200 mg twice daily (Y-axis etravirine plasma level in ng/ml; alleged target = 52 ng/ml).

237 h. The patient did not experience any adverse event on ETV.

Discussion

In the presence of normal hepatic function, the half-life of the nonnucleoside reverse transcriptase inhibitors (NNRTIs) are: nevirapine (NVP) 25–30 h and efavirenz (EFV) and ETV 35–40 h. ETV plasma levels are higher in HIV-negative individuals with mild-to-moderate hepatic impairment compared with healthy volunteers [1]. In HIV-positive individuals, hepatitis coinfection increases ETV area under the curve (AUC) at 12 h by about 1.35-fold [2].

In one study of 103 hepatitis C virus (HCV)/HIV-coinfected individuals who had fibroscan-defined mild-to-moderate (Child–Pugh A and B) cirrhosis, there was a positive correlation between liver stiffness and plasma levels of EFV and NVP; coinfected patients with compensated cirrhosis had higher than normal concentrations of NNRTIs, especially EFV [3].

Data from the DUET studies indicate that ETV pharmacokinetics do not vary by sex or race. Furthermore at the dose used, there was no clear relationship between pharmacokinetic parameters and efficacy or safety [2]. ETV is metabolized by hydroxylation by cytochrome P450 3A4 (CYP3A4) and the 2C family, followed by glucuronidation. To date, there are no data implicating specific genetic polymorphisms with ETV plasma concentrations. There is a high interindividual variability in ETV plasma levels [4].

EFV hepatic clearance in African–Americans is lower than in white non-Hispanic individuals [5]. In the 2NN study [6], lower EFV drug clearance was reported in Thai patients than in non-Asians, as well as a slightly higher rate of antiretroviral drug-associated adverse events.

There is a link between polymorphisms in CYP2B6 and EFV plasma level and central nervous system (CNS) side effects [7]. African–Americans and Hispanics have higher EFV AUC than European–Americans; EFV levels in African–Americans with the CYP2B6 homozygous G516T variant (TT) genotype were approximately three-fold higher than in individuals with the homozygous GG genotype. The same association was found in European–Americans with the TT genotype, although the frequency of this genotype is less than in African–Americans (16.7 versus 6.3%). Individuals with the TT genotype also had more CNS side effects in the first week of treatment with EFV.

Unlike EFV, NVP is metabolized by isoenzymes from both the CYP3A4 and CYP2B families [8], and polymorphisms in both have been shown to affect NVP levels [9,10].

Conclusion

Exact target ranges for ETV plasma levels have not been determined, and there is significant interpatient and intrapatient variability. ETV levels are mildly elevated in mild-to-moderate hepatic dysfunction. No data exist for severe hepatic dysfunction. This case showed excessive levels and a long half-life in severe liver disease at standard dosing without adverse outcome.

We present case evidence to support the ETV summary of product characteristics (SmPC) recommendation that pending further data, ETV should not be used in severe liver disease or decompensated liver cirrhosis.

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Received: 22 January 2009; accepted: 6 April 2009.

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DOI:10.1097/QAD.0b013e32832c9fb6

High rate of misclassification of treatment failure based on WHO immunological criteria

We read with interest the results reported by Reynolds *et al.* [1]. In a cohort of patients followed for a median (range) time of 20.2 (12.4–29.5) months, it was shown that the majority of patients with immunological criteria for treatment failure are virologically suppressed. The authors conclude that immunological monitoring alone could result in unnecessary switching to second-line treatment.

At the Infectious Diseases Institute (IDI) in Kampala, Uganda, viral load testing is performed only in the context of clinical trials due to cost; patients on antiretroviral therapy (ART) are clinically evaluated monthly and have $CD4^+$ cell count testing every 6 months. In January 2008, we sought to assess the validity of the WHO immunological criteria as a surrogate for virological failure by testing HIV viral load in clinic patients fulfilling the WHO criteria for ART failure: patients with a $CD4^+$ cell count of less than 100 cells/μl after 1 year on ART; patients with a 50% absolute $CD4^+$ cell count fall from the peak $CD4^+$ cell count while on ART; and $CD4^+$ cells per microlitre of baseline or less after 1 year on ART [2].

From the clinic database of more than 8000 patients who had ever initiated ART at IDI, we identified all patients who had received ART for at least 1 year and who fulfilled at least one WHO criterion for immunological failure. Viral load testing was performed at the next available clinic visit. An undetectable viral load was defined as 400 copies/ml or less.

We identified 4403 patients who had been on their first-line ART regimen for at least 1 year; 70% were initiated on a nevirapine and 30% on an efavirenz-containing regimen. A subset of 140 patients fulfilled at least one WHO criterion for immunological failure. Sixty-seven patients did not have viral load testing for the following reasons: four had died, 17 were lost to follow up, four were transferred, 22 had already switched to second-line ART because they fulfilled criteria for immunological failure, and 20 had already a viral load test. The remaining 73 patients underwent viral load testing. The median time on ART was 2.5 years (1.9–3.7 years), 37 (51%) patients were women, median [interquartile range (IQR)] age in years was 36 (30–40 years), and median $CD4^+$ cell count at evaluation was 43 cells/μl (11–113 cells/μl). The viral load results for these 73 patients are shown in Table 1. Overall, 52/73 (71%) of the patients tested had viral suppression. In the group of patients (18) that fulfilled more that one criterion for treatment failure, a substantial proportion of patients were also virologically suppressed (12, 66%).

Our results support the conclusions of Reynolds *et al.* [1] as well as previous reports from resource-limited settings (RLS) [3,4]. Overall, almost two-thirds of patients fulfilling at least one of the WHO criterion for immunological failure at a median of 2.5 years on first-line ART

Table 1. Viral load results for the 73 patients tested.

	Total	Viral load >400 copies/ml	Viral load ≤400 copies/ml (%)
All tested	73	20	52 (71)
Fulfilling one criterion	55	14	41 (75)
Fulfilling at least two criteria	18	6	2 (66)

had an undetectable viral load. Current WHO immunological criteria alone are insensitive in the diagnoses of treatment failure and may result in unnecessary switching to second-line therapy, which is both more costly and associated with greater adverse events. As an increasing number of patients begin to fail first-line ART in RLS, affordable viral load testing should be made available to confirm virological failure before switching patients to second-line therapy.

Acknowledgement

All the authors declare that they have conflicts of interest.

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Response to Castelnuovo *et al*. regarding our article 'Failure of immunologic criteria to appropriately identify antiretroviral treatment failure in Uganda'

The data of Castelnuovo *et al*. from an urban HIV clinic in Kampala confirm our report and other reports by colleagues in eastern Uganda that the current WHO monitoring guidelines are suboptimal [1–3]. The consistency of the findings underscores the importance of ongoing revision of current antiretroviral treatment monitoring guidelines with consideration of viral load testing to identify individuals failing therapy.

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Received: 9 April 2009; accepted: 9 April 2009.

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DOI:10.1097/QAD.0b013e32832cbd59