

Correspondence

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Acute porphyria precipitated by efavirenz

Whereas the association between HIV infection and porphyria cutanea tarda is well described [1], there is a paucity of data linking HIV infection, highly active antiretroviral therapy (HAART) and the acute hepatic porphyrias. We describe the first case of acute porphyria precipitated by the antiretroviral drug, efavirenz, presenting with back pain, sensory loss and anxiety.

A 39-year-old South-African man was diagnosed HIV-1 positive through sexual health screening in a London clinic. CD4⁺ cell count at diagnosis was 596 cells/ μ l (34%) and HIV viral load 331 copies/ml. Liver function tests were normal and he was hepatitis C antibody negative and hepatitis B surface Ag negative. He admitted to using the recreational drugs mephedrone and gamma hydroxybutyrate intermittently for 2 years but was taking no prescribed medication. After discussing the risks and benefits of starting HAART at his current CD4⁺ count, he was commenced on Atripla (emtricitabine/tenofovir/efavirenz) (Bristol-Myers Squibb, Uxbridge, UK & Gilead Sciences, Foster City, California, USA).

One month later, he presented to his local hospital with abdominal pain, generalized weakness and palpitations and was treated for viral gastroenteritis. He was discharged home 5 days later despite a plasma Na level of 125 mmol/l.

He was readmitted to our unit with a history of anxiety, back pain and altered sensation over his proximal legs and buttocks. He also complained of dark urine. On examination, he appeared anxious and tremulous with patchy sensory loss over the proximal aspects of his lower limbs with no motor impairment and normal anal tone. CD4⁺ cell count was 626 copies/ μ l and HIV viral load less than 40 copies/ml. Plasma sodium was 111 mmol/l. Thyroid function was normal (TSH 0.97 μ /l), serum and urine osmolality 287 mosm/k and 608 mosm/k compatible with the syndrome of inappropriate anti-diuretic hormone and liver function deranged (alanine transaminase 170 iU/l and bilirubin 27 μ mol/l). MRI imaging of his brain and spinal cord were normal.

The patient deteriorated over the subsequent week developing a progressive ascending motor neuropathy culminating in impaired ventilation requiring intubation. Lumbar puncture was performed revealing acellular cerebrospinal fluid (CSF) with normal biochemistry (CSF protein 0.37 g/l and CSF glucose 4 mmol/l, serum glucose 5.4 mmol/l) and negative microscopy and bacterial culture. CSF PCR for HSV1 and 2, Epstein-

Barr virus, varicella Zoster virus, cytomegalovirus and John Cunningham virus was negative. Electromyography and nerve conduction studies revealed acute and chronic motor axonal loss in proximal and distal upper and lower limb muscles with no evidence of demyelination.

Results of the urine analysis indicated increased excretion of 5-aminolaevulinic acid (ALA) [68.3 μ mol/mmol creat (normal range <3.8)] and porphobilinogen [38.2 μ mol/mmol creat (normal range <1.5)] confirming an acute porphyria. Atripla was stopped and the patient was treated with intravenous haem arginate. A subsequent diagnosis of variegate porphyria was made based on plasma fluorescence emission scanning (emission and excitation maximum 623 nm and 403 nm, respectively), and raised total coproporphyrin levels in the stool [204 nmol/g dry wt (normal range <46)].

The acute hepatic porphyrias (variegate porphyria, acute intermittent porphyria and hereditary coproporphyria) are a group of autosomal dominant disorders with incomplete penetrance characterized by enzyme deficiencies in the haem biosynthetic pathway that manifest as acute neurovisceral syndromes. Clinical features include abdominal and back pain, seizures, paralysis and autonomic disturbances including tachycardia and hypertension. A family history taken retrospectively confirmed the patient's maternal grandmother had been affected by porphyria. Drugs that induce the cytochrome P450 system, particularly CYPs 3A4 and 2C9 as together they constitute 50% of the human hepatic CYP-pool [2], are strongly porphyrinogenic. Activation of nuclear receptors by a range of ligands that includes drugs leads to concerted transcription of both the CYP-gene and hepatic 5-aminolavulaenic acid synthase (ALAS-1), which is the first and rate-limiting enzyme in the biosynthetic pathway [3,4]. The third enzyme in the pathway, hydroxymethylbilane synthase, is less abundant than the other haem synthesis enzymes [5] and becomes rate limiting when ALAS-1 is upregulated leading to toxic accumulation of porphobilinogen and ALA during acute attacks.

In the three previous reported cases of antiretroviral induced acute porphyria, the implicated offending agent has been nevirapine [6] and indinavir [7,8]. The most likely porphyrinogenic component of Atripla is efavirenz which is metabolized by CYP3A4 and both induce and inhibit this isoenzyme [9]; the former predominating during prolonged exposure which may in part explain the delayed presentation in our case.

Information on the porphyrinogenicity of drugs can be found on the Norwegian porphyria centre website [10] that currently classifies efavirenz as probably porphyrinogenic. Our patient has not been started on a new HAART regimen given his CD4⁺ cell count of 521 copies/ μ l and discussions regarding treatment will take place after rehabilitation has completed. The addition of raltegravir to the same nucleos(t)ide reverse transcriptase inhibitor backbone of emtricitabine/tenofovir is classed as probably nonporphyrinogenic and will likely form the basis of future therapy.

This case serves to remind us that HAART is not without its clinical risks particularly as more patients opt to start treatment early and the potential side-effects of taking medication in the individual need to be weighed carefully against the benefits.

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Apparent spontaneous clearance of chronic hepatitis C virus infection in a HIV co-infected patient with decompensated cirrhosis: a case report

Spontaneous clearance of chronic hepatitis C virus (HCV) infection is unusual, once chronic disease is established, particularly in HIV/HCV co-infected individuals [1]. In cirrhotic patients, pegylated interferon-based regimens achieve lower sustained virological response (SVR) rates and increase the likelihood of decompensation [2]. However, interferon-sparing regimens using novel direct-acting antivirals (DAAs) are now becoming available and have dramatically increased the SVR rates among cirrhotic patients, minimizing the risk of hepatic decompensation [3,4].

We report a patient with HIV/HCV co-infection and decompensated cirrhosis who appeared to have cleared HCV spontaneously on intensive investigation and, therefore, was not offered interferon-free treatment.

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A 43-year-old heterosexual man with a history of prior intravenous drug use was initially diagnosed with HIV-1 infection in 2008 in the context of *Pneumocystis jirovecii* pneumonia. At baseline, he had a CD4⁺ cell count of 30 cells/ μ l, plasma HIV RNA of 39 911 copies/ml, positive anti-HCV (Abbott Architect; Abbott Diagnostics, Abbott Park, Illinois, USA) and confirmed HCV genotype 4 infection by sequencing (Micropathology Ltd, Coventry, UK) with a plasma HCV RNA level of 602 745 IU/ml (Abbott Real Time HCV PCR, M2000 system; Abbott Diagnostics). He was later shown to be IL28B-CC genotype. Screening demonstrated past hepatitis B virus (HBV) infection with negative surface antigen and undetectable HBV DNA. Combination antiretroviral therapy (cART) with emtricitabine/tenofovir/efavirenz (200/300/600 mg) once daily was initiated

shortly after HIV diagnosis and, by 1 year of treatment, his CD4⁺ cell count had improved to 310 cells/ μ L. Soon afterwards, he developed decompensation of his chronic liver infection in the form of ascites, jaundice and mild encephalopathy (Child–Pugh B). A liver biopsy showed florid periportal bile duct reaction, marked lobular inflammation and fibrosis scoring 4/6. A decision for HCV treatment was deferred whilst the patient attempted

to reduce his high BMI. Regular alpha-fetoprotein levels, liver ultrasound and MRI scans were performed without evidence of hepatocellular carcinoma.

His cirrhosis progressed to Child–Pugh C and the patient was referred for liver transplantation, which was turned down due to a low predicted 5-year survival, an assessment influenced by the patient's refusal to receive

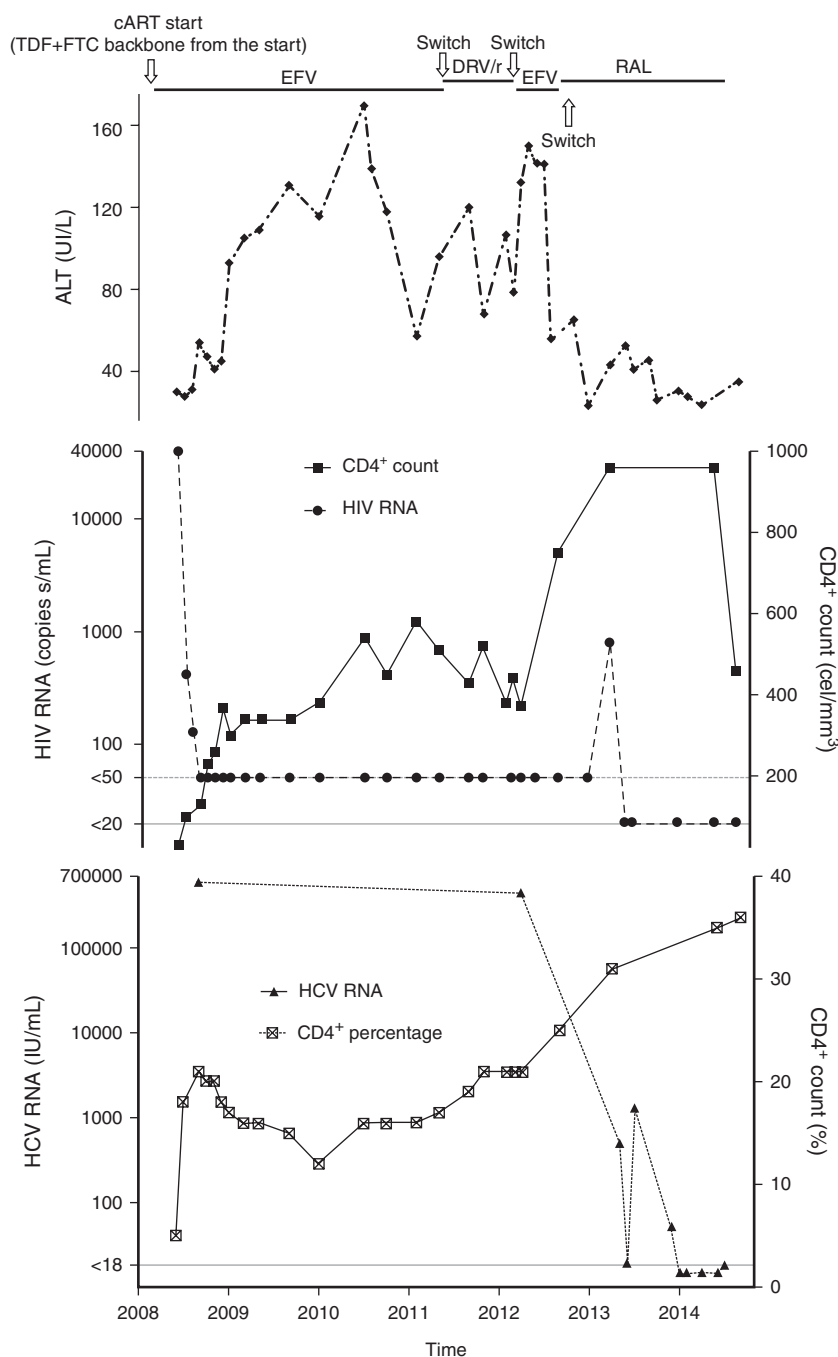


Fig. 1. Time trends from HIV presentation in May 2008 for antiretroviral regimes (with fixed nuke-backbone maintained throughout regimes) and laboratory results: ALT, HCV RNA, HIV RNA, absolute CD4⁺ cell count and CD4⁺ percentage. ALT, alanine transaminase; cART, combined antiretroviral therapy; DRV/r, darunavir/ritonavir; EFV, efavirenz; FTC, emtricitabine; HCV, hepatitis C virus; RAL, raltegravir; RNA, ribonucleic acid; and TDF, tenofovir.

blood products according to his beliefs as a Jehovah's witness.

His liver function deteriorated further despite medical management. To minimize drug interactions in case of transplantation and/or HCV treatment, efavirenz was switched to raltegravir 400 mg twice daily in January 2013. Around that time, plasma HCV RNA levels experienced a downward trend, achieving values of less than 15 HCV RNA IU/ml (Roche Cobas TaqMan; Roche Molecular Diagnostics, Pleasanton, California, USA) in January 2014. At that time, he was considered for early access to DAA therapy (sofosbuvir with either ledipasvir or daclatasvir). Subsequently, no HCV RNA was detected on three occasions (February, April and June 2014). In parallel, CD4⁺ cell count increased from 370 cells/ml (21%) in April 2012, to 955 cells/ml (31%) in June 2014 (Fig. 1).

A transjugular liver biopsy was performed showing evidence of inactive cirrhosis, mild portal and nodular inflammation, no large cell or fatty change, negative stains for iron and alpha-1 antitrypsin consistent with resolved infection and no evidence of HCV RNA on PCR (Micropathology Ltd). An HCV-specific enzyme-linked ImmunoSpot that assessed interferon- γ production in peripheral blood mononuclear cells (stimulated by gt1 and gt4 HCV peptides) at this time was not reactive, suggesting recovery of CD8⁺ and CD4⁺ T-cell immunity was not responsible for his HCV clearance.

Spontaneous clearances of established HCV infection have been previously described in absence of specific anti-HCV CD4⁺ responses [5]. Although rare, HCV clearance among HIV-HCV co-infected patients on cART is mainly described in patients with IL-28B CC genotype, suggesting this subset of patients might benefit from an earlier initiation of cART [1,6–9]. The initial period of HCV undetectability coincided with a switch to raltegravir and a marked increase in peripheral CD4⁺ cell count. Whether this was causal is unclear. However, maintained HIV viral suppression [10] and improvements in drug-associated hepatotoxicity have been described in cirrhotic HCV-HIV co-infected patients after switching to raltegravir [11].

What makes this case more unusual is that, given the potential availability of novel DAAs to a limited number of patients, invasive liver investigation was undertaken, which not only failed to find virus, but also showed little evidence of active infection. Cases such as this one raise important implications for patients with very advanced disease being considered for DAA therapy. The potential for low-level viraemia, and even prolonged periods of aviraemia, is well recognized [12]. Whether in these patients more invasive investigations are helpful to exclude the possibility for a hidden focus of HCV infection is unclear. It remains uncertain as to whether, in

the absence of viraemia, the likelihood of persistent viral reservoirs should be sufficient to justify treatment.

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An unexpected interaction between warfarin and cobicistat-boosted elvitegravir

Elvitegravir, cobicistat, emtricitabine, and tenofovir (Stribild) is a co-formulated once-daily tablet approved for the treatment of HIV type 1 (HIV-1) antiretroviral therapy (ART)-naïve adult patients [1]. Elvitegravir is also available as a single entity, but requires co-administration with cobicistat, a pharmacokinetic booster, or the protease inhibitor, ritonavir, for adequate antiretroviral plasma concentrations [2]. Cobicistat is a potent inhibitor of cytochrome P450 isoenzyme 3A4 (CYP3A4) and P-glycoprotein, and increases the concentration of concurrently administered medications, leading to a number of drug interactions and contraindicated medications [1,3,4]. Unlike other integrase inhibitors, elvitegravir induces CYP2C9 and may lead to decreased concentrations of concurrently administered medications cleared via this isoenzyme [1,2]. Little is known regarding elvitegravir's clinical effects on co-administered CYP2C9 substrates.

Warfarin is a racemic mixture consisting of two enantiomers. The S-enantiomer is approximately three to four times more potent and undergoes metabolism primarily by CYP2C9 [5]. The R-enantiomer is less potent and is primarily metabolized by CYP1A2, CYP3A4, and CYP2C19 [5]. It is not known whether warfarin induction or inhibition will occur when administered concurrently with elvitegravir and/or cobicistat, respectively.

HIV-1 infection is associated with an increased risk of venous thromboembolism, making concomitant anticoagulation common with ART [6]. Due to many drug interactions between antiretrovirals and the novel anticoagulants, warfarin is most commonly used in HIV-positive patients requiring indefinite anticoagulation [7]. We report a possible interaction between elvitegravir and warfarin in a patient receiving a stable warfarin dose for the preceding 2 years [8].

A 42-year-old Caucasian man with a medical history significant for HIV-1 infection and recurrent bilateral lower extremity deep venous thromboembolism requiring indefinite anticoagulation [goal international normal-

ized ratio (INR) 2.0–3.0] was followed in the infectious diseases clinic. ART consisted of once-daily co-formulated efavirenz 600 mg, emtricitabine 200 mg, and tenofovir 300 mg. During this time, his weekly warfarin dose was stable at 50 mg for approximately 2 years (Fig. 1). The patient maintained an excellent virologic and immunologic response [HIV PCR <20 copies/ml; CD4⁺ = 714 (34%)], but requested an alternative ART regimen as he continued to experience efavirenz-induced central nervous system dysphoria. The ART regimen was changed to once-daily co-formulated elvitegravir 150 mg, cobicistat 150 mg, emtricitabine 200 mg, and tenofovir 300 mg. The patient's warfarin regimen was not preemptively altered due to uncertainty in quantitative INR effects. After 14 days on elvitegravir/cobicistat, the warfarin dose remained stable. One week later (on day 20 after elvitegravir/cobicistat initiation), the patient's INR became subtherapeutic (Fig. 1). The patient's warfarin dose was gradually increased to 80 mg per week in order to maintain a therapeutic INR. No other medication changes occurred during this transition. The patient's warfarin weekly dose has remained stable for the subsequent 10 months with concurrent elvitegravir/cobicistat.

Drug interactions between ART and warfarin are well known [9]. A small retrospective case-control study compared 18 patients receiving concurrent ART with warfarin [efavirenz (*N* = 7), ritonavir-boosted protease inhibitor (*N* = 8), and concomitant non-nucleoside reverse transcriptase inhibitor with a protease inhibitor (*N* = 2)] to 36 control (warfarin only) patients [10]. The mean daily warfarin dose was 3.5 mg higher in case patients. No difference in the daily warfarin dose was seen in case patients for the various ART regimens. In the present case, the patient historically maintained a therapeutic INR on an average warfarin daily dose of 7.1 mg with an efavirenz-based ART regimen. The warfarin daily dose increased to 11.4 mg with elvitegravir-based ART. The patient's warfarin requirement and INR values did not change initially, which may have been confounded by efavirenz's long elimination half-life when elvitegravir was initiated. Additionally, hepatic

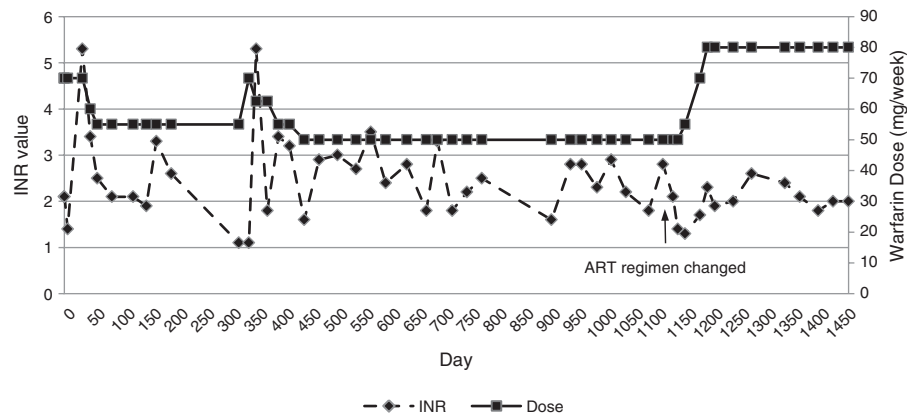


Fig. 1. Warfarin dose. Change in weekly warfarin dose and resulting INR values over time before and after elvitegravir/cobicistat was initiated.

CYP induction is usually delayed and primarily has its maximum effects within 1–2 weeks after an inducer is added [11]. These effects were demonstrated in the present case as warfarin titration began on day 20. In this case, elvitegravir CYP2C9 induction appears to have the stronger effect on warfarin metabolism as compared to CYP3A4 inhibition by cobicistat. This patient required a 60% warfarin dosage increase, which is similar to previous studies [10,12]. This interaction is unique to elvitegravir as raltegravir and dolutegravir do not have any known CYP induction or inhibition effects [13,14]. On the basis of this case, patients receiving concomitant warfarin and elvitegravir therapy should have close INR monitoring with an expected need for dose titration.

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Lack of evidence for the selection of E138 mutations by first-generation non-nucleoside reverse transcriptase inhibitors in patients infected with HIV-1 non-B subtypes

Understanding the mechanisms and predictors of drug resistance development to HIV-1 antiretroviral therapy (ART) is a key challenge to further improve HIV-1 treatment strategies and prevent epidemic spread. The extensive genetic diversity characterizing the HIV-1 pandemic, classified into groups, subtypes and recombinants, has been shown to affect viral escape from drug-selective pressure and influence treatment decisions [1]. In previous issues of *AIDS*, Crawford and colleagues reported the selection of mutations E138A/G/K/Q upon treatment failure with first-generation non-nucleoside reverse transcriptase inhibitors (NNRTIs) efavirenz (EFV) or nevirapine (NVP) in patients infected with subtypes A1, D and recombinant form A2D [2,3]. Amino acid substitutions at polymorphic position E138 in the reverse transcriptase enzyme recently acquired clinical relevance by their association with reduced in-vitro activity and in-vivo response to second-generation NNRTIs etravirine and rilpivirine [4–7]. Crawford *et al.* [2] reported their findings as unique given that, in their dataset, mutations at E138 were selected in non-B subtype viruses and upon treatment exposure with first-generation NNRTIs.

HIV-1 genotypic complexity challenges the identification and interpretation of resistance-associated mutations, and we feel that the confounding effect of HIV-1 epidemiology weakens their claims, which are not sufficiently supported, provided the reported study design. Crawford and colleagues report the occurrence of mutations E138A/G/K/Q in 12.1% (respectively, 6.1%, 2.6%, 1.7%, and 1.7%) of 115 patients failing therapy with resistance mutations at resistance testing. It is well established that evidence for selection of a mutation by a specific drug requires genotypic information both before drug exposure and at viral breakthrough. In the study by Crawford and colleagues, data on baseline mutational patterns in drug-naïve patients were missing and there was no acknowledgement of the polymorphic nature of this codon position, with mutations occurring naturally at frequencies that vary according to the viral subtype [8,9]. Therefore, from the information presented, it is not possible to discriminate between two plausible hypotheses: independent selection of these mutations due to convergent evolution under drug pressure with first-generation NNRTIs or their presence as natural polymorphisms prior to therapy initiation.

Before the advent of second-generation NNRTIs, E138 mutations were not systematically monitored in HIV-1 resistance studies. By then, selection of E138 mutations by NVP and EFV was less well documented, and only patchy information was available on a phenotypic impact towards first-generation NNRTIs [10,11]. The wide and long-standing use of EFV and NVP has resulted in abundant

genotypic data on NNRTI-containing regimens, with E138 mutations present at the time of treatment failure. However, this is no proof for its selection upon treatment exposure [8]. In fact, a recent study by Sluis-Cremer *et al.* [9], comparing E138A prevalence according to treatment experience in large patient populations infected with subtype B and C viruses, showed that E138A is polymorphic in drug-naïve patients and that E138A frequency is not strongly affected by prior RTI exposure. Apart from drug pressure, a high prevalence of E138 mutations in specific patient populations could be due to human leukocyte antigen (HLA)-restricted cytotoxic T lymphocyte (CTL) pressure, with certain HLA-carrying individuals having a higher prevalence of the natural polymorphism E138A [12], due to local transmission clusters of a particular viral variant [13] or due to founder effects created by subtype-specific epidemics.

While we argue that evidence for selection with first-generation NNRTIs is insufficiently supported, the selection of E138 mutations by second-generation NNRTIs has been observed and described in clinical isolates. However, evidence is available for its selection in various HIV-1 subtypes, and not exclusively in subtype B, in contrast to what has been stated [1]. Whereas research and drug design were historically skewed towards HIV-1 subtype B, dominant in developed countries, there has been an increased attention for the challenges of HIV-1 diversity and specifically the impact of globally predominating non-B subtypes on resistance development. As such, knowledge on subtype-specific mutations and pathways has been acquired from genotypic and phenotypic analyses of major HIV-1 subtypes, with subtype differences being acknowledged by expert-based drug resistance interpretation systems [14–16]. We therefore feel that the claimed paradigm of antiretroviral drug resistance mutation patterns and resistance algorithms being derived from in-vitro and clinical studies of subtype B viruses and infections is no longer valid.

In conclusion, insufficient evidence was provided for the original claim of E138 mutation selection by first-generation NNRTIs in non-B subtypes given that a baseline drug-naïve population was not studied and that potential subtype, geographical origin or host effects were not considered. We suggest that additional analyses should be performed to validate the hypothesis of subtype-dependent selection of E138A/G/K/Q by in-vivo treatment with EFV and NVP.

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