waned until D26, when he began to show initial improvement. Unresolved AMS led to the discontinuation of posaconazole on D28, and subsequently the serum level from that day measured 20 h after the last dose was found to be 3650 ng/mL, with a concurrent voriconazole serum level of <0.1 mg/L. Following the discontinuation of posaconazole, the patient had prompt resolution of AMS. He was continued on liposomal amphotericin B for his invasive fungal sinusitis. Notably, on D48, 300 mg posaconazole DR tablets were resumed and the patient tolerated this therapy without CNS complications. Table 1 depicts the sequence of azole administration, the serum levels and the evolution of AMS.

In our recent experience at MD Anderson Cancer Center, over 15% of patients on posaconazole DR tablets had serum levels >4000 ng/mL without apparent CNS toxicity, suggesting that higher levels alone are not predictive of CNS toxicities.[5] We hypothesize that our patient experienced synergistic triazole toxicity while on posaconazole due to concurrent supratherapeutic voriconazole serum levels. We hypothesize that, as a substrate of CYP3A4, voriconazole metabolism may have been inhibited by the initiation of posaconazole, a potent CYP3A4 inhibitor, potentially resulting in prolonged voriconazole exposure despite its discontinuation. However, AMS did not resolve until posaconazole was discontinued, even at low voriconazole levels. Posaconazole-induced phospholipidosis in neurons has been reported, but the potential mechanisms behind posaconazole CNS toxicity remain to be elucidated.[6] The fact that CNS toxicity did not occur on posaconazole rechallenge supports the notion that posaconazole DR tablets may be associated with CNS effects through lowering of a neurotoxicity threshold by concurrent exposure to other CNS-compromising agents such as voriconazole. In conclusion, use of posaconazole DR tablets may be associated with CNS effects when the toxicity threshold is lowered by concurrent exposure to other CNS-compromising agents such as voriconazole at supratherapeutic concentrations.

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Dolutegravir-induced hyperglycaemia in a patient living with HIV

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Sir,

Diabetes mellitus (DM) type II is an important cause of morbidity and mortality among persons living with HIV (PLWH).[1,2] Treating PLWH is often complicated due to side effects associated with ART and comorbidities. Hyperglycaemia is common with PIs, though this side effect has become less prominent with the development of newer ART.[3] Although side effect profiles have improved, practitioners must know if patients are at an increased risk of fluctuations in serum plasma glucose from ART, especially newer agents.[1]

We report the case of an African-American male living with HIV who switched to abacavir/lamivudine and dolutegravir after 16 years of treatment with abacavir/lamivudine and efavirenz due to neuropsychiatric effects attributed to efavirenz. His medical history included HIV (CD4 cell count 598 cells/mm^3 and HIV RNA <20 copies/mL), chronic kidney disease stage 4, DM type II (baseline HbA1c <6.2% and fasting plasma glucose 65 mg/dL), hyperlipidaemia, hypertension, Crohn's disease and sinusitis. The patient's maintenance medications aside from ART included lorazepam,

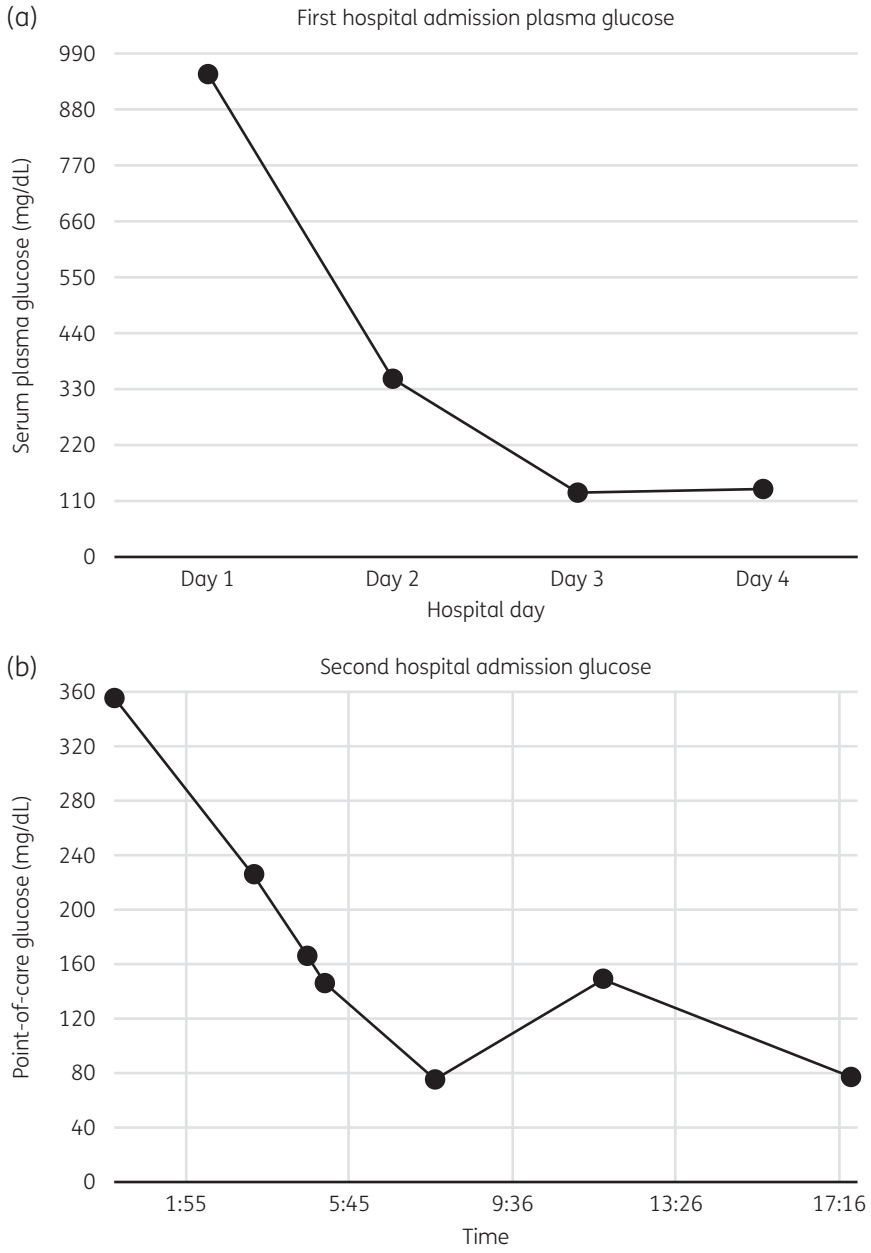

Figure 1. Hospital admission plasma glucose: (a) first admission; and (b) second admission.

aspirin, glyburide, metoprolol succinate, omeprazole, risperidone, atorvastatin, lisinopril, fluticasone propionate nasal spray and diltiazem, all of which he had been taking for at least 5 years.

Approximately 3 weeks after the switch from efavirenz to dolutegravir, the patient presented to the emergency department (ED) with polyuria, polydipsia and visual changes. The results of initial evaluations showed that the patient had developed hyperglycaemia. Pertinent labs included: plasma glucose level, 949 mg/dL; serum creatinine, 5.26 mg/dL; and HbA1C, 14.9%. The patient was initially treated with normal saline, insulin lispro and insulin glargine. The patient was discharged after 4 days when his serum plasma glucose stabilized on his current home medications with the addition of nateglinide and insulin glargine (Figure 1a). No clear cause for hyperglycaemia was identified including active infections. The patient noted a blood glucose of approximately 180 mg/dL upon arrival home. Shortly after eating dinner, he reported a post-prandial blood glucose of ∼380 mg/dL and he returned to the ED 1 day post-discharge where his blood glucose was 355 mg/dL. The patient reported that he had filled all of his discharge medications and was taking them as prescribed. The patient was later discharged after his blood glucose was stabilized (Figure 1b). Insulin lispro was added to his previous discharge medications and his ART remained unchanged. At this time, the patient self-discontinued dolutegravir and his self-reported blood glucose measurements improved. His DM remained well controlled with insulin glargine, insulin lispro and nateglinide. Three weeks after

discharge, dolutegravir was switched to ritonavir-boosted atazanavir by the patient's infectious diseases provider. Pertinent labs at this follow-up visit included: fasting plasma glucose level, 67 mg/dL; serum creatinine, 3.86 mg/dL; and HbA1C, 8%. Three months after follow-up, the patient's HbA1C was 6%.

The recent change from efavirenz to dolutegravir may have been the likely cause of this patient's hyperglycaemia. There has been one other report of integrase strand transfer inhibitor (INSTI)-induced hyperglycaemia thus far in the literature of an Asian-American male with no prior history of DM.[4] The patient had experienced polyuria, polydipsia, blurred vision, fatigue and weight loss 4 months after he was switched to abacavir, lamivudine and raltegravir from abacavir, lamivudine and efavirenz. A mechanism for the INSTI-induced hyperglycaemia was hypothesized to be due to chelation of magnesium, thereby inhibiting the release and signalling of insulin.[4]

Several clinical trials have demonstrated the efficacy of dolutegravir.[5] Of these trials, hyperglycaemia is reported in SPRING-2, SAILING, SINGLE and VIKING-3.[6–9] Information regarding plasma glucose abnormalities was located on clinicaltrials.gov and the package insert for the SPRING-2 study.[8,10] A similar frequency of grade 2 hyperglycaemia (serum plasma glucose level between 126 and 250 mg/dL) was seen in 6% of both dolutegravir and raltegravir participants. Grade 3 hyperglycaemia (serum plasma glucose level >251 mg/dL) was experienced in <1% and 2% of the dolutegravir and raltegravir groups, respectively. In the SAILING study, grade 3 hyperglycaemia (uncontrolled hyperglycaemia despite treatment modification or hospitalization) and grade 4 hyperglycaemia (life-threatening consequences such as ketoacidosis, hyperosmolar non-ketotic coma and end-organ failure) were experienced in 1% of dolutegravir and 2% of raltegravir participants.[6]

Hyperglycaemia was represented as a laboratory abnormality with a worsening grade from baseline in ≥2% of participants in the SINGLE study.[9] The dolutegravir/abacavir/lamivudine group had 9% in the grade 2 hyperglycaemia classification (serum plasma glucose between 126 and 250 mg/dL) and 2% in the grade 3 classification (serum plasma glucose >251 mg/dL), whereas the efavirenz/tenofovir/emtricitabine group had 6% in the grade 2 hyperglycaemia classification and <1% in the grade 3 classification.[10] Hyperglycaemia was not mentioned in the original VIKING-3 trial; however, it was included in the package insert.[7,10] Hyperglycaemia was one of the most common treatment-emergent laboratory abnormalities in treatment-experienced subjects, observed in 14% at week 48.[10]

Although an uncommon occurrence, hyperglycaemia is a potential side effect of dolutegravir. Healthcare professionals should be aware of this rare but serious event. Close monitoring of serum plasma glucose should be considered after initiation of an INSTI.

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