Infection (2019) 47:115–119
https://doi.org/10.1007/s15010-018-1201-x

CASE REPORT

Overdose of elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide in an HIV-1-infected subject with attempted suicide

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Received: 4 July 2018 / Accepted: 21 August 2018 / Published online: 25 August 2018

Abstract

Introduction Data are lacking regarding overdose of Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide (E/C/F/TAF).

Material and methods We present the first report of suicidal attempt with E/C/F/TAF in a Human Immunodeficiency Virus-infected subject.

Results A reversible acute renal failure with no proximal tubulopathy and neuropsychiatric issues are discussed. E/C/F/TAF withdrawal resulted in favourable renal and neuropsychiatric outcomes. The suicide attempt seemed unrelated to the integrase strand transfer inhibitor, being evenly explained within the context of stressful personal conflicts.

Conclusion A suicidal attempt with an E/C/F/TAF overdose in an HIV-infected patient, resulted in a favourable outcome from a renal and neuropsychiatric standpoint.

Keywords Elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide · Overdose · Suicide attempt

Elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (E/C/F/TAF) is a recommended initial or switching antiretroviral treatment (ART) with a favourable renal and bone safety profile, in current guidelines [1, 2]. Conflicting data have been recently reported regarding the potential association between neuropsychiatric adverse events and integrase strand transfer inhibitors (INSTIs) [3, 4]. Data are lacking concerning renal or neuropsychiatric outcomes in E/C/F/TAF overdoses. We present hereunder a case report of a suicide attempt by E/C/F/TAF overdose (30 tablets) in a Human Immunodeficiency Virus (HIV)-infected subject.

A 51-year-old Caucasian man was admitted to the hospital after being found unconscious by his wife. He had been diagnosed with HIV infection 5 years before, with a nadir 139 CD4+ T cells/mm^3 and plasma HIV-1 RNA 722,000 copies/mL, a wild-type genotype B HIV-1 with CCR5 tropism; HLA-B*5701 was negative. He had started ART with efavirenz plus emtricitabine/tenofovir disoproxil fumarate (TDF) in 2012, without developing any neuropsychiatric adverse event. Due to vitamin D deficiency, hypophosphatemia and osteopenia, ART was switched to E/C/F/TAF 9 months before admission. His current CD4+ T-cell count was 587 cells/mm^3 and plasma HIV-1 RNA 38 copies/mL.

He was a smoker, denied the use of recreational drugs and did not take concomitant medication. He worked as a coach driver and reported a huge burden of stress due to a leading and responsible position at work.

On admission, he had recovered his consciousness spontaneously (without specific drug antagonist) and presented with an apathetic attitude and was sparing with his words. He did not complain about abdominal pain, nausea or vomiting and the abdomen was not tender or distended. He looked well, alert, oriented to time, place and person, no

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focal neurologic signs, normal hydration and breathing, no skin or mucosal lesions, normal cardiac and breath sounds.

He reported a voluntary intake of 30 tablets of E/C/F/TAF (estimated cumulative dose: 4.5 g of elvitegravir, 4.5 g of cobicistat, 6 g of emtricitabine and 300 mg of tenofovir alafenamide) plus roughly 10 tablets of lorazepam 1 mg (his mother´s regular medication), 12 h before. He received activated charcoal by oral gavage and a few unidentified tablets were recovered from gastric lavage. Drug abuse testing in the urine revealed only benzodiazepines.

He recognised a suicidal ideation in the setting of personal and labour conflicts, resulting in judicial problems. His wife, family and working environment were unaware of his HIV status and this caused him increasing anxiety due to fear of discrimination. Trust and nonjudgmental support measures were created to facilitate the patient's HIV status disclosure to his wife.

Potential toxicity associated with exposure to plasma E/C/F/TAF overdose was monitored. We estimated an exposure to at least 20-fold the maximum therapeutic dose, considering that only a few tablets had been recovered from the gastric lavage.

Blood tests revealed a progressive renal impairment (serum creatinine on admission was 0.92 mg/dL), achieving a serum creatinine peak of 2.15 mg/dL (estimated glomerular filtration rate by Chronic Kidney Disease Epidemiology Collaboration, $eGFR_{CKD\text{-}EPI}$, 34.4 mL/min/1.73 m^2), within the first 48 h after admission. A urine analysis showed a few hyaline casts without proteinuria and a kidney ultrasound was unremarkable. Normal plasma creatine kinase levels ruled out rhabdomyolysis. Despite the well-hydrated status of the patient at the time of assessment on admission, the estimated time of stupor could have been about 12 h, which could have compromised his intravascular volume due to decreased fluid intake. Intravenous fluidotherapy was instituted and renal function reached a plateau and returned to baseline 2 weeks after, without any evidence of residual renal damage. Based on laboratory findings and clinical evolution, hypothesis of acute tubular necrosis was made as the primary mechanism of renal function impairment.

No data suggestive of an underlying chronic mental (affective or psychotic) or personality disorder were revealed in the evaluation by psychiatry, apart from the adjustment disorder. No new neuropsychiatric signs appeared during his stay, potentially attributed to the high elvitegravir exposure. Mirtazapine, a sedative antidepressant drug, was started to relieve the situational anxiety and to improve sleep. The patient kept a hermetic although collaborative attitude, without subsequent suicide ideation.

The ART was empirically switched to ritonavir-boosted darunavir plus abacavir/lamivudine.

Six months later, the patient kept a good general condition, was encouraged and geared to work and family environment, maintaining mirtazapine therapy. Blood tests displayed 706 CD4+ T cells/mm^3, plasma HIV-1 RNA 53 copies/mL, creatinine 0·77 mg/dL ($eGFR_{CKD\text{-}EPI}$, 105.1 mL/min/1.73 m^2) and no proteinuria.

To the best of our knowledge, this is the first report of a suicidal attempt with an overdose of E/C/F/TAF in humans. The case was reported to the National Pharmacovigilance Center.

A previous report of suicidal attempt with an overdose of dolutegravir in combination with TDF and emtricitabine, showed reversible renal impairment and no Fanconi syndrome [5].

Due to higher intracellular concentrations of tenofovir (TFV) achieved with TAF (5–7 times higher than those with TDF) within target peripheral blood mononuclear cells (90% lower systemic TFV exposure), fewer off-target effects are expected, pointing to reduced renal or bone adverse events [6]. In addition, TAF does not interact with organic anion transporters (OAT)-1 or OAT3 on the basolateral membrane of renal proximal tubule, impeding its dose-dependent accumulation.

It is known that cobicistat inhibits multidrug and toxin extrusion protein-1 (MATE-1), a drug transporter on the apical membrane of renal proximal tubule cells that results in reduced tubular secretion of creatinine, leading to increases in serum creatinine and reductions in creatinine clearance, with no effect on actual GFR as measured by clearance of iohexol [7]. Accordingly, a low impact on renal damage should be expected with higher TAF and cobicistat doses.

In virologically suppressed subjects switching from a previous TDF and boosted agent-containing regimen to E/C/F/TAF, estimated glomerular filtration rate by Cockcroft–Gault ($eGFR_{CG}$) values increased in the TAF group (median 1·2 mL per min, IQR −6·6 to 9·1) compared with decreases from baseline in the TDF group (median −3·7 mL per min, IQR −10·5 to 3·5) between week 2 and week 48 ($p < 0{\cdot}0001$) [8].

The long-term results of clinical trials support the use of E/C/F/TAF in HIV-infected patients with mild–moderately impaired renal function ($eGFR_{CG} \geq 30$ mL/min). Through 96 weeks, there was no decrease in median $eGFR_{CG}$ either whether patients were switched from a TDF- or non-TDF-based regimen or whether baseline $eGFR_{CG}$ was < 50 or ≥ 50 mL/min [9].

Of note, no cases of proximal renal tubulopathy (including Fanconi syndrome) have been reported in 7595 participants included in TAF-based regimens of a recent pooled analysis of 27 phase II/III clinical trials of TAF versus TDF or abacavir [10] and particularly, in none of 2437 participants included in overall studies involved in E/C/F/TAF development phase III clinical trials [8, 9, 11–15].

No data are available on overdoses of E/C/F/TAF in humans [16]. The E/C/F/TAF package insert and

manufacturer include data about isolated doses of elvitegravir, cobicistat, emtricitabine and TAF equivalent to 2, 2·7, 6 and 12·5 times, respectively, the dose in E/C/F/TAF in healthy subjects. No severe adverse reactions were reported. The effects of higher doses or the administration of the coformulation are unknown. Treatment of the overdose consists of general supportive measures. As elvitegravir and cobicistat are highly bound to plasma proteins, it is unlikely that they will be significantly removed by hemodialysis or peritoneal dialysis. Regarding emtricitabine, hemodialysis removes approximately 30% of the dose over a 3-h hemodialysis period starting 1.5 h of emtricitabine dosing. Tenofovir is efficiently removed by hemodialysis, with an extraction coefficient of approximately 54%. However, it is worth noting that TAF primarily undergoes hepatobiliary clearance and is minimally eliminated in urine as unchanged drug. In this regard, E/C/F/TAF has recently showed safety and tolerability in 55 HIV-1-infected subjects with $eGFR_{CG} < 15$ mL/min on chronic hemodialysis and dose adjustment was not required. Pharmacokinetic data demonstrated that plasma concentrations of TAF were consistent with the ranges of historical data in HIV-1-infected patients with normal renal function [17].

In our patient, ART withdrawal and fluidotherapy were enough for recovering renal function.

INSTIs have recently been associated with potential neuropsychiatric adverse events. Our patient was receiving elvitegravir.

Suicidal ideation and behaviour is acknowledged in the current Food and Drug Administration (FDA) label information (adverse reactions retrieved from randomised clinical trials (RCTs)) of all four available INSTIs [16, 18–20], particularly in subjects with pre-existing history of psychiatric illness.

First data reported about probable association between an INSTI-containing ART regimen and neuropsychiatric events, were obtained with dolutegravir [3], but contradictory data have been reported since. In a large German cohort, the rate of discontinuation of dolutegravir because of neuropsychiatric adverse events (the most frequent of which were sleep disturbances), was significantly higher than for other INSTIs (raltegravir or elvitegravir), by 5.6% within 12 months of initiation. Of note, in almost all patients the symptoms occurred during the first few weeks on DTG; symptoms disappeared quickly after discontinuation in most of them, but symptoms resolved despite continuing DTG in several of them. Almost threefold higher discontinuation rates were observed amongst women and older than 60 years patients, population underrepresented in clinical trials. Patients initiating abacavir at the same time, despite prior negative human leukocyte antigen (HLA) B * 5701 testing, also discontinued more frequently [21]. In a Spanish prospective cohort, there was a low rate of discontinuations due to neuropsychiatric adverse events with dolutegravir, but dolutegravir was more frequently discontinued than either raltegravir or elvitegravir. A higher rate of discontinuations for older subjects was not found [4].

In contrast, headache (7%) and insomnia (5%) were the most common nervous system adverse events reported in HIV-1 infected and virologically suppressed subjects switching to E/C/F/TAF in a RCT [8]. Premature adverse events-related discontinuation was reported in < 1% of patients, including a suicidal attempt and depression in a patient each (out of 959 patients in the TAF arm). In addition, two completed suicides, one suicidal ideation [22, 23] and one suicide attempt [24] have been reported within the E/C/F/TDF arms included in RCTs.

Of note, a meta-analysis of phase III RCTs in treatment-naïve subjects, comparing whichever INSTI to efavirenz and protease inhibitors was conducted by the FDA. It did not show differences in risk for neuropsychiatric adverse events, and no increased risk was attributable to INSTIs [25].

Scale for Suicide Ideation (SSI) [26] and Suicide Intent Scale (SIS) [27] were applied to our patient 4 days after admission. The total score of evaluation suggested low risk of suicidal ideation and behaviour. The event was unplanned and the patient did not recognise prior use of illicit toxic substances. The trigger of the event was considered a stressful personal conflict, conferring to ART toxicity a lower weight as potential underlying role. In addition, absence of development of new-onset neuropsychiatric adverse events with the drug overdose, would point against a correlation or causality relationship between drug exposure and neuropsychiatric symptoms [28]. In this sense, we cannot rule out that mirtazapine could have contributed to attenuate symptoms such as anxiety or insomnia, but the antidepressant effect would not be expected to appear in such a short time.

A limitation of our report was that plasma drug concentrations were not monitored at the time of drug overdose exposure.

In conclusion, a suicidal attempt with an E/C/F/TAF overdose in an HIV-infected patient resulted in a favourable outcome from a renal and neuropsychiatric standpoint.

A moderate reversible acute renal failure was seen, with no proximal renal tubulopathy or Fanconi syndrome, consistent with the results retrieved from TAF- and E/C/F/TAF-development RCTs. No new psychiatric signs were seen. These data suggest that the suicide attempt was probably not related to the drug, but rather it could evenly be explained in the setting of an adjustment disorder.

Author contributions Concept and drafting of the manuscript: HA and JML critical revision of the manuscript: AM, NV, JG-G, HD-C the authors approved the final version of the manuscript.

Compliance with ethical standards

Conflict of interest Hortensia Álvarez has received support for attending meetings from Janssen-Cilag, Gilead Sciences, ViiV Healthcare, AbbVie, and Merck Sharp and Dohme. Ana Mariño has received support for attending meetings from Bristol-Myers Squibb, Gilead Sciences, Janssen-Cilag and ViiV Healthcare. Josep M. Llibre has received grants from ViiV Healthcare and has received honoraria and consulting fees from Gilead Sciences, Merck Sharp and Dohme, Bristol-Myers Squibb, and ViiV Healthcare, all them outside the submitted work. The remaining authors declare no relevant conflicts of interest to the content of the manuscript.

Human rights statement This is a research involving a human participant. The patient provided written consent for publication of his clinical record.

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