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Liquorice-Induced Pseudohyperaldosteronism with Severe Hypokalaemia in a Young Patient Living with HIV: A Rare Case Presentation and Literature Review

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Abstract

Background: HIV-1 infection treatment has greatly improved with the availability of combined antiretroviral therapy (cART). Unlike Tenofovir Disoproxil Fumarate, Tenofovir Alafenamide has a more favourable renal profile, even if proximal tubulopathy and electrolyte disturbances have been reported. As earlier as 4000 years ago, liquorice root was used for some medical treatments. Excessive liquorice intake is described to cause a state of mineralocorticoid excess. However, liquorice-induced hypokalaemia usually occurs with mild clinical manifestations and a severe presentation is rare.

Case presentation: We report a case of a 33-year-old woman admitted to our Emergency Unit with diagnosis of severe hypertension and acute headache. She had a story of HIV since 2011 and was taking cART (Darunavir/Cobicistat/Emtricitabine/Tenofovir Alafenamide) with a stable viro-suppression. She was an active smoker, occasional drinker, and admitted a large intake of liquorice for at least one year (2.5-3 mg/Kg/daily). At physical examination, high blood pressure, tachycardia, and lower limb paraesthesia with paraparesis were observed. A severe hypokalaemia (K^+<1.5 mmol/L) associated with metabolic alkalosis, and high creatine kinase (CK) levels were found, with an estimated potassium chloride deficit of 650 mEq. Electrocardiogram showed ST depression, T waves flattening, and prominent U waves.

The prompt administration of intravenous MgSO4 and KCl supplementation led to a rapid improvement of muscular symptoms and electrocardiographic features and, during hospitalization, we observed a progressive blood pressure stabilization, electrocardiogram normalization and muscular symptoms complete remission with CK values lowering to normal range. The patient was discharged ten days after admission, asymptomatic, with normal blood pressure and potassium values.

Conclusions: we reported the first case of severe hypokalaemia due to possible interplay between cART regimen and liquorice intake. It could be of some interest given that liquorice is increasingly used also as adjuvant to antiviral therapy.

Keywords: Hypokalaemia; Pseudohyperaldoteronism; HIV; Combined Antiretroviral Therapy; Liquorice Intake

Introduction

Human Immunodeficiency Virus -1 (HIV-1) infection treatment has greatly improved over years with the introduction of combined antiretroviral therapy (cART) [1]. Among cART regimens, Darunavir/Cobicistat/Emtricitabine/Tenofovir Alafenamide (Symtuza®) showed a more favourable renal and bone profile, even if proximal tubulopathy and electrolyte disturbances are reported [2].

As earlier as 4000 years ago, liquorice root was used for some medical treatments [3]. The major bioactive principle is glycyrrhizic acid, which has been shown to inhibit the enzyme 11-β- hydroxysteroid dehydrogenase decreasing the conversion of cortisol to the inactive form [4]. Consequently, this could cause pseudo-hyperaldosteronism with hypokalaemia, hypertension, and metabolic alkalosis. Excessive liquorice intake is described to cause a state of mineralocorticoid excess [5]. However, liquorice-induced hypokalaemia usually occurs with mild clinical manifestations and a severe presentation is rare.

We described, for the first time, a case of liquorice-induced pseudo-hyperaldosteronism with severe hypokalaemia occurred in a young HIV patient on ART treatment.

Case presentation

A 33-year-old woman was admitted to our Emergency Unit with severe hypertension and acute headache. Fifteen days earlier, she was evaluated by her infectious diseases' physician, who observed generalized muscular weakness and paraesthesia especially involving lower limbs and suggested a neurological examination in order to rule out a possible neuropathy. Regarding her history of HIV, she received the diagnosis in 2011 at 24 years and had a severe AIDS presentation (*Pneumocistis jiroveci* pneumonia, disseminated cytomegalovirus disease, oral candidiasis, chronic muco-cutaneus Herpes simplex). The CD4+ T-cell nadir count was 33 cell/mL. After the initiation of cART with a boosted darunavir-based regimen, she experienced an excellent viro-immunological response. During follow-up, she received different boosted-darunavir based regimens (along with tenofovir disoproxil fumarate and abacavir-lamivudine). Since 2019, she received a new cART formulation (Darunavir/Cobicistat/Emtricitabine/Tenofovir Alafenamide) with a stable viro-suppression (HIV RNA was undetectable since 2011 and latest CD4 T-cell count available was 626 in 2020). Moreover, her medical history revealed post-surgical hypothyroidism for benign toxic goitre on levothyroxine replacement therapy and mild anaemia on iron and acid folic supplementation. She reported being an active smoker, occasional drinker, and admitted a voluptuary use of pure liquorice in granules for at least one year. She was not able to exactly quantify the daily liquorice amount, but according to what she declared, we could estimate that she assumed 2.5-3 mg/Kg/daily.

Physical examination showed lower limb paraesthesia with paraparesis, high blood pressure (200/100 mmHg) and tachycardia (100beats/min). Neurological examination was not conclusive for any organic pathology. Laboratory findings are reported in Table 1.

A severe hypokalaemia (K^+<1.5 mmol/L) was found and was confirmed through a venous blood gas analysis (K^+1.49 mmol/L), in association with metabolic alkalosis (pH 7.53, bicarbonates 53 mmol/mol), and high creatine kinase (CK) levels (13211 U/L). Potassium chloride (KCl) deficit was estimated to be about 650 mEq.

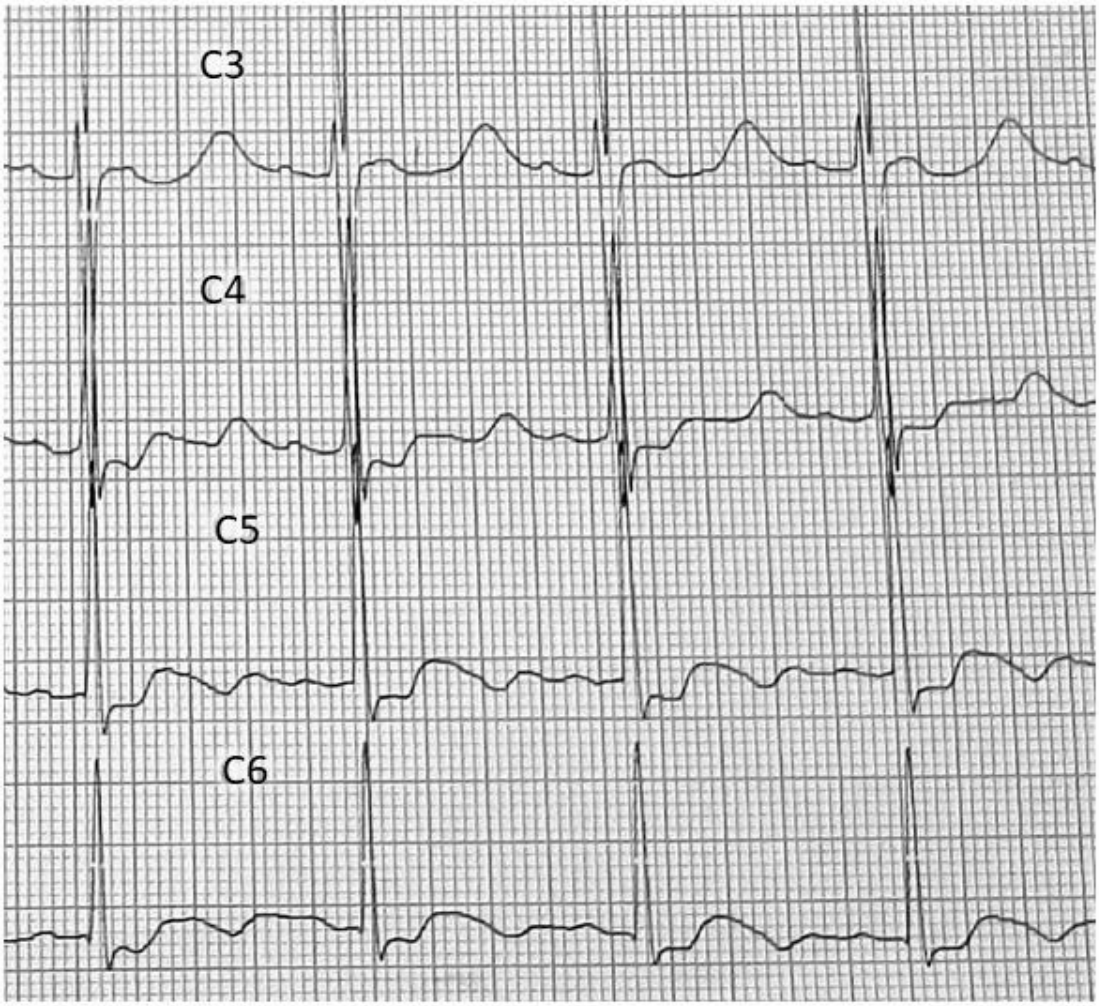
The patient denied previous history of hypertension or hypokalaemia, episodes of diarrhoea, vomiting or laxative/diuretic use/abuse.

Electrocardiogram (ECG) at admission (Figure 1) showed, besides a mild right bundle branch block, ST depression, T waves flattening and prominent U waves, more evident in precordial leads.

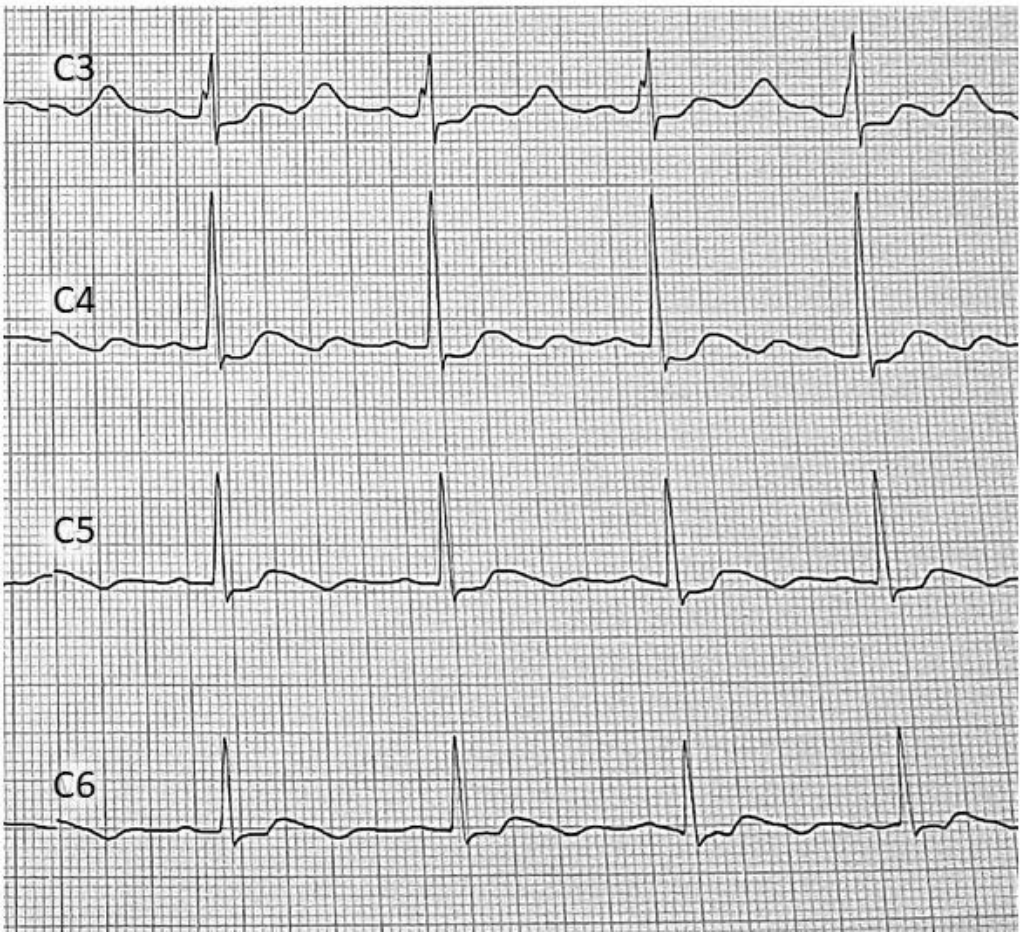
Intravenous MgSO4 and KCl supplementation was promptly administered with a rapid improvement of muscular symptoms and ECG features (Figure 1).

She was admitted to our Endocrine-Metabolic Unit for further diagnostic work-up and treatment. Hormonal profile revealed normal aldosterone levels, very low renin values and normal cortisol levels (Table 1). No abdominal or adrenal masses were found at ultrasound evaluation.

During hospitalization we noticed an overall improvement of the patient's clinical condition, with a progressive electrocardiogram normalization, CK values normalization and muscular symptoms remission. Blood pressure was restored to normal values through the introduction of amlodipine and potassium canrenoate. The patient was discharged ten days after admission, asymptomatic, with normal blood pressure and potassium values (Table 1). She was prescribed to continue therapy with oral potassium canrenoate and potassium chloride supplementation in addition to her home therapy, and to absolutely avoid liquorice intake.



a) At admission, K^+ 1.49 mmol/L



b) During KCI supplementation, K^+ 2.2 mmol/L

Figure 1: (a) ECG findings (precordial leads C3 to C6) at admission, with correspondent K+ value; ECG showed mild right bundle branch block, ST depression, T waves flattening and prominent U waves; **(b)** ECG findings (precordial leads C3 to C6) during KCl supplementation, with correspondent K+ value; progressive normalization of ECG features

Parameter	Values at admission	Values at discharge	Normal laboratory range
Sodium (Na)	144	139	136-145 mmol/L
Potassium (K)	<1.5	4.3	3.4-4.5 mmol/L
Chloride (Cl)	84	104	98-107 mmol/L
Alanine aminotransferase (AST)	223	25	10-35 U/L
Aspartate aminotransferase (ALT)	508	60	18-34 U/L
Gammaglutamyltransferase (GGT)	9	/	6 – 42 U/L
Creatine kinase (CK)	13211	181	26-192 U/L
Total bilirubin	0.4	0.55	<1.2 mg/dL
Creatinine	0.9	0.82	0.6-1 mg/dL
Glucose	113	91	78-106 mg/dL
Calcium (Ca)	8.5	8.98	8.6-10.2 mg/dL
Lactic dehydrogenase (LDH)	882	430	135 – 225 U/L
Aldosterone	5.7	/	1.2-23.6 ng/dL
Renin	<2	/	2.8 - 39.9 μUI/ml
Cortisol	13.6	/	4.8 - 19.5 μg/dL

Table 1: Laboratory findings at patient's admission and at discharge

Discussion

The treatment of HIV-1 infection has greatly improved over the years with the introduction of combined antiretroviral therapy (cART) [1]. Nowadays, despite the absence of a definitive cure, the natural history of the disease is radically changed, and it is considered a chronic yet manageable disease [6]. Among cART regimens, Darunavir/cobicistat/emtricitabine/tenofovir alafenamide (Symtuza®) was the first protease inhibitor (PI)-based single-tablet regimen (STR) available for the treatment of adults and adolescents (aged ≥ 12 years) with HIV-1 infection [2]. Unlike Tenofovir Disoproxil Fumarate, Tenofovir Alafenamide has a more favourable renal and bone profile even if proximal tubulopathy and electrolyte imbalance are reported [2].

Liquorice (Glycyrrhiza glabra) has been used since ancient times both as sweetener and as medical remedy (hypotension and stomach ulcers) [3,7]. In literature, many reports of severe complications due to large ingestion of liquorice amount have been reported [8,9].

The pathophysiology of the clinical effects of liquorice has been well investigated, and it depends mainly on glycyrrhizic acid, the active component of liquorice, which inhibits 11β-hydroxysteroid dehydrogenase, an enzyme implied in cortisol conversion to cortisone [4,8]. The subsequent cortisol excess is responsible of the apparent mineralocorticoid excess [5,7]. This clinical syndrome is similar to primary aldosteronism, and presents with hypokalaemia, hypertension, metabolic alkalosis and low plasma renin. However, unlike primary aldosteronism, plasma aldosterone levels are low [10].

The severity of clinical presentation of hypokalaemia mainly depends on the degree and the duration of low serum K^+ level, as recently showed by Kwon YE et al. [11], who found that patients with lower limbs paraparesis and/or paralysis had serum K^+ level below 2 mEq/L, as shown in our case. Of note, the muscular symptoms and CK elevation found in our patient may be explained not only for the very low K+ values, but they may also be related to HIV infection and the ongoing cART regimen. In fact, CK elevation in HIV infected patients may have a multifactorial pathogenesis in up to one third of cases, including HIV-associated inflammatory myopathy, medications, alcohol abuse, and drug overdose [12].

Despite our observation, it has been reported [13] that liquorice consumption is rarely associated with serum K+ levels <2.0mmol/L. This is also due to the fact that, as reported by the Scientific Committee on Food [14], one can safely ingest regular large amount of glycyrrhizic acid (approximately 2 mg/Kg/die) without adverse effects. Furthermore, a significant individual variation is observed in the susceptibility to glycyrrhizic acid-induced adverse effects [11]. Unfortunately, we were not able to exactly quantify the daily liquorice amount consumed by our patient, but according to what she declared, we could estimate that she assumed 2.5-3 mg/Kg/daily for voluptuary use. Taking into account the above considerations, it is unlikely that liquorice *per se* could be responsible for the severe hypokalaemia (K^+<1.5 mmol/L), with KCl deficit estimated of about 650 mEq, as found in our patient.

On the other hand, Tenofovir Disoproxil Fumarate alone or in combination with other drugs (especially boosted protease inhibitors) is associated with an increased risk over time of renal tubular abnormalities, causing hypokalaemia [15-18]. Speculating on this issue, we believe that the severity of clinical presentation of our patient could be due to the concomitant interplay between liquorice intake and cART regimen treatment. This potential interplay is noteworthy since liquorice has emerged, especially in traditional Asian medicine, as an antiviral agent, and recently, the combination of tenofovir and glycyrhizin was investigated in patients with chronic hepatitis B with beneficial effects [19]. The glycyrrhetinic acid, the main active metabolite of glycyrrhizin, was shown to be a strong inhibitor of Glycoprotein P (P-gp) [20], which is a membrane, bound efflux protein that can be a substrate for Tenofovir alafenamide. This may theoretically lead to an increased Tenofovir alafenamide plasmatic concentration, even if the Liverpool HIV drug interactions database [21] did not investigate this possible interaction, and no interaction was found also between liquorice and emtricitabine, that the patients was taking, together with darunavir and cobicistat. With respect to latter drugs, glycyrrhizin is a mild CYP3A4 inducer, thus potentially decreasing the bioavailability of darunavir, but this occurrence is unlikely given the stronger inhibitory effect of cobicistat on CYP3A4 [22].

It would have been interesting to test plasmatic concentrations of antiretrovirals during the clinical event, but unfortunately it was not possible. Moreover, there is a single report to date about the possible interaction between liquorice and a boosted PI (atazanavir), but no clinical relevance was found [23].

Furthermore, with particular regard to HIV, glycyrrhizin was described to both inhibit cell-free viral infection and cell to cell infection, and also HIV replication. Moreover, it was suggested that the antiviral effects of glycyrrhizin could be linked to immune activation induction [24-26]. Based on these considerations, and also because since 1989 glycyrrhizin has been tested in AIDS patients [27], it would have been interesting to investigate the potential correlation between the levels of inflammation, e.g. by measuring some cytokines, and the treatment of liquorice-induced hypokalaemia, but unfortunately cytokine dosage was not available. Of note, our patient did not assume liquorice in order to boost of antiviral activity or the ongoing cART.

It is well known that some clinical events non-AIDS related can occur in HIV-infected patients [28]. For this reason, clinicians involved in the care of people living with HIV need to be aware the several clinical conditions may occur and lastly, that polypharmacy is an actual issue in HIV-infected ageing people, but also in younger ones [29].

Conclusion

This report describes a case of severe hypokalaemia due to interplay between cART regimen and liquorice intake. It is important to underline that, therapeutic reconciliation, i.e. investigating the intake of any substance (not only conventional drugs) is an important part of clinical follow-up in order to assess the presence of possible drug-interactions.

Authors' Contributions

IP and CC did the data collection; LC and EF wrote the primary draft. RZ, AF and CC were involved to interpret the patient data and edit the manuscript. All the authors have read and approved the manuscript.

Availability of Data and Materials

Data sharing is not applicable to this article as no dataset were generated or analysed during the current study.

Consent of Publication

Written informed consent for publication of her clinical details and clinical images was obtained from the patient.

Competing Interests

The Authors declare that they have no competing interest.

References

1. Samji H, Cescon A, Hogg R (2013) Closing the gap: increases in life expectancy among treated HIV-positive individuals in the United States and Canada. PLoS One 8: e81355.

2. Deeks ED (2018) Darunavir/Cobicistat/Emtricitabine/Tenofovir Alafenamide: A Review in HIV-1 Infection. Drugs 78: 1013-24.

3. Shibata S (2000) A drug over the millennia: pharmacognosy, chemistry, and pharmacology of licorice. Yakugaku Zasshi 120: 849-62.

4. Farese RV Jr, Biglieri EG, Shackleton CH, Irony I, Gomez-Fontes R (2012) Licorice-induced hypermineralocorticoidism. N Engl J Med 325: 1223-7.

5. Omar H, Komarova I, El-Ghonemi M (2012) Licorice abuse: time to send a warning message. Ther Adv Endocrinol Metab 3: 125-38.

6. Deeks SG, Lewin SR, Havlir DV (2013) The end of AIDS: HIV infection as a chronic disease. Lancet 82: 1525-33.

7. Attout H, Randriajohany A, Josse F, Appavoupoule V, Thirapathi Y (2020) Tetraparesis with Major Hypokalaemia and Rhabdomyolysis Induced by Chronic Liquorice Ingestion. Eur J Case Rep Intern Med 7: 001375.

8. Penninkilampi R, Eslick EM, Eslick GD (2017) The association between consistent licorice ingestion, hypertension and hypokalaemia: a systematic review and meta-analysis. J Hum Hypertens 31: 699-707.

9. Nazari S, Rameshrad M, Hosseinzadeh H (2017) Toxicological Effects of Glycyrrhiza glabra (Licorice): A Review. Phytother Res 31: 1635-50.

10. Pandher R, Puvanendran A, Diamond TH (2020) The dangers of herbal teas: hypertension and weakness caused by liquorice-induced apparent mineralocorticoid excess. Med J Aust 213: 207-8.

11. Kwon YE, Oh DJ, Choi HM (2020) Severe asymptomatic hypokalemia associated with prolonged licorice ingestion: A case report. Medicine (Baltimore) 99: e21094.

12. Koubar SH, Estrella MM, Warrier R (2017) Rhabdomyolysis in an HIV cohort: epidemiology, causes and outcomes. BMC Nephrol 18: 242.

13. Lin SH, Yang SS, Chau T (2003) Halperin ML An unusual cause of hypokalemic paralysis: chronic licorice ingestion. Am J Med Sci 325: 153-6.

14. Europa C (2003) Food, S.C.o. Opinion of the scientific committe on food on glycyrrhizinic acid and its ammonium salt, Europe.

15. Albini L, Cesana BM, Motta D (2012) A randomized, pilot trial to evaluate glomerular filtration rate by creatinine or cystatin C in naive HIV-infected patients after tenofovir/emtricitabine in combination with atazanavir/ritonavir or efavirenz. J Acquir Immune Defic Syndr 59: 18-30.

16. Tai C, Chou RY, Guo J, Chen HP (2020) Severe acute hypokalaemia associated with piperacillin/tazobactam in an HIV-infected

patient under antiretroviral therapy with tenofovir alafenamide: case report and literature review. Sex Health 17: 194-7.

17. Koratala A, Ruchi R (2017) Hypokalemia: A potentially life-threatening complication of tenofovir therapy. SAGE Open Med Case Rep 14: 2050313X17741010.

18. Calza L, Trapani F, Tedeschi S (2011) Tenofovir-induced renal toxicity in 324 HIV-infected, antiretroviral-naïve patients. Scand J Infect Dis 43: 656-60.

19. Hung CH, Kee KM, Chen CH (2017) A Randomized Controlled Trial of Glycyrrhizin Plus Tenofovir vs. Tenofovir in Chronic Hepatitis B with Severe Acute Exacerbation. Clin Transl Gastroenterol 8: 104.

20. Huan C, Xu Y, Zhang W (2021) Research Progresson the Antiviral Activity of Glycyrrhizin and its Derivatives in Liquorice. Front Pharmacol 12: 680674.

21. Hiv-Druginteractions (2010) Liverpool HIV Pharmacology Group [database on the Internet] Cheshire, United Kingdom: The University of Liverpool and eMed- Fusion, UK.

22. Sherman EM, Worley MV, Unger NR (2015) Cobicistat: Review of a Pharmacokinetic Enhancer for HIV Infection. Clin Ther 37: 1876-93.

23. Cheng BH, Zhou X, Wang Y (2015) Herb-drug interaction between an anti-HIV Chinese herbal SH formula and atazanavir in vitro and in vivo. J Ethnopharmacol 162: 369-76.

24. Fiore C, Eisenhut M, Krausse R (2008) Antiviral effects of Glycyrrhiza species. Phytother Res 22: 141-8.

25. Sun ZG, Zhao TT, Lu N, Yang YA, Zhu HL (2019) Research Progress of Glycyrrhizic Acid on Antiviral Activity. Mini Rev Med Chem 19: 826-32.

26. Hosseinzadeh H, Nassiri-Asl M (2015) Pharmacological Effects of Glycyrrhiza spp. and Its Bioactive Constituents: Update and Review. Phytother Res 29: 1868-86.

27. Hattori T, Ikematsu S, Koito A (1989) Preliminary evidence for inhibitory effect of glycyrrhizin on HIV replication in patients with AIDS. Antiviral Res 11: 255-61.

28. Lapadula G, Chatenoud L, Gori A (2015) Risk of Severe Non AIDS Events Is Increased among Patients Unable to Increase their CD4+ T-Cell Counts >200+/µl Despite Effective HAART. PLoS One 10: e0124741.

29. Focà E, Magro P, Guaraldi G (2019) Elderly HIV-positive women: A gender-based analysis from the Multicenter Italian "GEPPO" Cohort. PLoS One 14: e0222225.