Title: Development of Iatrogenic Cushing’s syndrome in a patient on Anti-Retroviral Therapy

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Introduction

Glucocorticoids (GC) are used for variety of indications in human immune deficiency virus (HIV) infected population, including chronic respiratory diseases and musculoskeletal conditions. A majority of prescribed and endogenous GC are metabolized by cytochrome-P450. Antiretroviral therapy (ART) used for the treatment of HIV infection can have significant interaction with other drugs. ART combinations include pharmacologic boosting agents that inhibit cytochrome-P450, thus increasing the plasma levels of these drugs. Subsequent increase in plasma concentrations of the prescribed GC can induce iatrogenic Cushing’s syndrome (ICS) and through the hypothalamic pituitary adrenal (HPA) axis feedback mechanism, ICS leads to secondary adrenal suppression and low endogenous cortisol levels. There are multiple reports in HIV patients developing ICS and adrenal insufficiency as a result of drug-drug-interactions with inhaled or intranasal GC therapy. But repor ts related to intra-articular triamcinolone injections causing ICS are relatively uncommon.  
  
Case report

We describe a 55-year-old white female with acquired HIV infection on a single tablet regimen Genvoya™ (Elvitegravir, Cobicistat, Emtricitabine, and Tenofovir-Alafenamide) who was hospitalized following a road traffic accident requiring knee surgery. Post-operative course was complicated by joint infection requiring intravenous ertapenem for three months. Due to persistent knee pain, she received 40 mg triamcinolone-acetate intra-articular injection every 3 months for a total of three injections. She presented seven months later with symptoms including new onset diabetes, hypertension, fatigue, easy bruising and poor wound healing. On physical examination, she appeared obese with moon facies, buffalo hump, supraclavicular fullness, facial flushing and multiple ecchymosis over extremities. On laboratory evaluation, HIV viral load remained undetectable since onset of ART and CD4 count was within normal range. Endocrine workup showed suppressed endogenous HPA axis [low cortisol (1.1 u g/dL) with low ACTH levels (1.1pg/mL)], thus confirming ICS. Due to concern for drug-drug-interaction between the Cobicistat component of her ART regimen and intra-articular GC, Genvoya™ was switched to Dolutegravir and Emtricitabine/Tenofovir-alafenamide and intraarticular GC administration was discontinued. Upon re-evaluation six months later, her symptoms improved significantly and she did not require hydrocortisone replacement. In conclusion, she developed ICS followed by secondary adrenal suppression due to systemic absorption of triamcinolone-acetate and decreased CYP3A metabolism by cobicistat.

Conclusion  
Cobicistat and ritonavir are pharmacokinetic boosters that prolong the action of other ART drugs via CYP3A inhibition that also enhances GC affect. The effect of cobicistat is not widely known compared to ritonavir. The potential for interaction with GC can occur with any non-systemic routes of administration (intra-nasal, inhaled or intra-articular) and when used together, patients should be monitored for ICS and secondary adrenal insufficiency. We emphasize the importance of awareness of serious drug-drug-interactions before introducing new medications in patients on ART.