

Iatrogenic Cushing syndrome secondary to enhanced protease inhibitors: Case report and review

Vernon De Maynard

ABSTRACT

Introduction: Human Immunodeficiency Virus (HIV+ve) positive patients taking enhanced Protease Inhibitors (ePI) can develop Iatrogenic Cushing Syndrome (ICS) and adrenal insufficiency that did not appear to be associated with intralesional, intra-articular, inhaled or intranasal, topical glucocorticoid therapy. Given the expected reduction in the patient's capacity to remove cortisol from the body a high index of clinical suspicion is required for diagnosis. **Case Report:** This paper describes a 58-year-old man whose HIV ceased to be well-controlled on ePI-based Anti-Retroviral Therapy (ART) twice, and who developed Cushing syndrome-like symptoms including keloid scars and faecal incontinence in association with a chronic cortisolaemia. **Conclusion:** Enhanced protease inhibitors have proven an important course of treatment in the fight against HIV/AIDS. However; these very powerful drugs can have unintended consequences that are not very well documented. As stress and its relation to cortisol are well documented, future should attempt to examine the relationship between perceived stress and HIV viral load and determine how serum cortisol might mediate the relationship between psychological stress and viral load in patients taking ePI ART.

Keywords: Acquired immune deficiency syndrome, Enhanced protease inhibitors, Human Immunodeficiency Virus, Iatrogenic cushing syndrome, Stress

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INTRODUCTION

Second-tier antiretroviral therapy (ART) for those living with Human Immunodeficiency Virus (HIV) often involves the use of enhanced protease inhibitors (ePIs) such as 'Ritonavir' or 'Cobicistat' boosted 'Darunavir' in combination with other antiretroviral drugs (ART) such as entry inhibitors, nucleoside reverse transcriptase inhibitors (NRTI), non-nucleoside reverse transcriptase inhibitors (NNRTI), or integrase inhibitors. As protease inhibitors are highly metabolised in the gut, the bioavailability is enhanced using drugs that inhibit their reduction via Cytochrome P450 (CYP3A4) pathway [1]. Unfortunately, the CYP3A4 pathway is also important for the reduction of serum cortisol. At times of psychological stress HIV-positive patients taking enhanced ePIs may not be able to get rid of the cortisol produced; resulting in hyperglycaemia, pathological hypertension, fungal infections, weight gain, mood changes, osteonecrosis, and suppressed immune system. There is some evidence in the literature of some HIV-positive patients developing Iatrogenic Cushing's Syndrome (ICS) and adrenal insufficiency after receiving intraarticular and epidural triamcinolone injections [2, 3]. but determining how much enhanced protease inhibitors ART contributes to variance in serum cortisol and viral load in isolation of triamcinolone is, unclear. The paper describes case of a 58-year-old HIV-positive man who developed ICS

unrelated to intralesional 'Triamcinolone' injections while taking ePI included ART. The author will explore the potential relationship between serum cortisol and enhanced protease inhibitors in HIV-positive people, and argue that serum cortisol might mediate the relationship between psychological stress and viral load.

CASE REPORT

A 58-years-old HIV-positive man, who had been living with HIV for over 20 years, was prescribed ritonavir-boosted protease inhibitor-based antiretroviral therapy (ART) or enhanced protease inhibitors (ePI ART) due viral mutation and detectable viral load (12,000 copies/mL) which had previously been undetectable. His CD4⁺ T Cell count remains on around 300/ μ L on average. Approximately 3–4 months after beginning ePI ART, he developed Iatrogenic Cushing syndrome (ICS) and relative secondary adrenal insufficiency (SAI) unrelated to any glucocorticoid therapy such as intralesional, intranasal or intraarticular triamcinolone injection.

Patient's medical history

In February 2016, the patient's ARV was changed to enhanced protease inhibitors, (i.e., Ritonavir 100 mg, Darunavir 800 mg, and Truvada (200 mg of Emtricitabine and 245 mg of Tenofovir disoproxil), due to loss of antiviral control due to virus mutation, (i.e., viral load was 12,000 copies/mL). Unfortunately, shortly after beginning this new regimen the patient complained of Cushing's-like symptoms, (i.e., increased fat on face, arms, legs, abdomen back of the neck, hypertension, stretch marks, keloid scars, mood swings, and marked loss of libido), compounded by phlebotomy-associated keloid scars, erythematous gastritis and duodenitis, pedal and rectal oedema, and reduced anal sphincter control and faecal incontinence with urinal frequency and urgency of unknown origin. Further examination, using MRI defaecating spectrogram, flexible sigmoidoscopy and endoanal ultrasound scans in May 2016, did not reveal any evidence of pelvic floor weakness. However, there was evidence of small solitary rectal syndrome, grossly reduced gut motility, severely compacted transverse, sigmoid and rectal colon, and grossly attenuated internal and external sphincter complex, idiopathically. Sacral neuromodulation with a colostomy bag was offered as a treatment for this unexplained faecal incontinence, but declined because the patient felt that 'he was managing with the 'Peristeen' (Coloplast, UK) anal plugs and rectal irrigation, and the surgeons seemed more interceded in carrying out surgery rather than find a solution to his problems'. In June 2016, the patient complained of adverse reaction to the enhanced ARV therapy, and offered a different combination of enhanced protease inhibitors to be taken daily, (i.e., Rezolsta (Cobicistat 150 mg and Darunavir 800 mg), and Truvada (200 mg of Emtricitabine and 245 mg of Tenofovir disoproxil).

In January and May 2017, the keloid scars on the patient's forearms were treated with Triamcinolone 10 mg/mL, intralesionally. Serum cholesterol was found to be 646 and 588 nmol/L; however, his 24 urine cholesterol was low, (i.e., 57 nmol/L). The adverse symptoms persisted until the patient refused to take any more enhanced protease inhibitors and requested an alternative ART at the end of December 2017. An ART involving Maraviroc 300 mg bd, Dolutegravir 50 mg bd, and Rilpivirine 25 mg/d commenced the first week of January 2018. Serum cholesterol had reduced to 248 nmol/L in February 2018. An overnight dexamethasone suppression test in April 2018 revealed that the patient was now able to suppress serum cortisol to twenty-one nmol/L. In May 2018, the patient was diagnosed with hepatosteatois, hyperglyceridaemia (HDL: cholesterol ratio = 4.93), increased abdominal fat, and BMI of 37.2, and advised to reduced dietary fats and sugars and increase exercise and begin statins due to increased risk of diabetes. In June 2018, anorectal physiology tests indicated a significant improvement in anal sphincter control, (i.e., maximum resting pressure increased from zero in May 2016 to 40 mmHg in June 2018). In July 2018, the patient's triglycerides were elevated at 3.2 mmol/L, HDL/cholesterol ratio = 6.21, and the three-month average plasma glucose concentration, (i.e., glycated haemoglobin (HbA1c IFCC) was raised at 50 mmol/L (6.7% of haemoglobin has become chemically-bonded with glucose). A statin, Atorvastatin (40 mg daily) was prescribed to deal with the hepatosteatois, but it severely reduced the patient's ability to do exercise, and he stopped taking it after six weeks preferring to continue trying to reduce his HbA1c to less than 42.1 mmol/L (6%) by diet and exercise alone.

Unfortunately, shortly after beginning this new regimen the patient complained of increased fat on face, arms, legs, abdomen back of the neck, hypertension, stretch marks, keloid scars, mood swings, and marked loss of libido which further debilitated the patient. An unexplained paralysis of the bowel and loss of anal sphincter control further compounded the patient's loss of self-esteem and confidence and confounded any confidence in the clinicians' ability to care for the patient as a passive recipient of health and social care. Every time the patient needed to give a blood sample, the venflon (and often more than one was needed) used left a keloid scar. The fact that the phlebotomist seemed to be reluctant to believe that the patient was an intravenous drug abuser did not help his self-esteem and willingness to engage with the health services. The reduced self-esteem and need to stop people thinking that he was an intravenous drug abuser prompted the patient to try and have the scars removed with an intralesional steroid injection to treat. The fact that the numerous objective tests did not result in clinicians choosing to review the ART and prescribe an alternative ART without the patient refusing to take any more ePI, left the patient - traumatised. The trauma manifested as agoraphobia, panic and anxiety. For instance, the patient described the difficulty he had

answering the door to visitors, answering the phone or emptying the mailbox, seeing clinicians, and coming up with 101 reasons to return home when out the shopping. His sense of panic was further demonstrated when he returned home rather than get stranded, and not being able to hail a taxi, or fit his bicycle into a taxi. In the end, the patient was left feeling that the HIV mutation was his fault, and that the ensuing difficulties experienced with the enhanced protease inhibitors were his fault, and that it was unsafe even dangerous to continue being a passive recipient of health care. The patient now insists on playing a more active role in his health care which means that he actively participates in the decision-making based on information he insists clinicians have shared with him, (i.e., co-construction of care rather than simply accepting whatever is offered).

DISCUSSION

The patient's pathology suggests that he had significant morbidity, (i.e., fatty liver, herpes simplex virus, hypertension, bilateral ulnar and carpal tunnel syndrome, achilles and tibialis posterior tendinopathy and plantar faciopathy, and persistent fungal throat infections), before the onset of ART. It would not be unreasonable to suggest that these symptoms would have happened irrespective of the HIV due to age and genetics, and that proportion of the variance in the severity of these symptoms that may be attributed to HIV is unclear. The deciding factor as to whether to start ART was the very low CD4⁺ T cell count, (i.e., 32 T cells/mL), and the increased risk of opportunistic infections such as pneumocystis pneumonia, microsporidium and parasites. The introduction of the integrase and nucleoside reverse transcriptase inhibitors ART to boost the CD4⁺ T cell count and reduce the viral load to zero was successful for five years, but they were undoubtedly complicit in the onset of gynecomastia and exacerbation in peripheral neuropathy. The treatment for acute Hepatitis C, or HIV, or a combination of both, may have contributed significantly to pathological hypertension observed, and may have contributed the loss of bone causing the enamel of the teeth to crack and flake off and the teeth to become "loose" in the jaws over such a short space of time. Curiously, the use of Triamcinolone to treat an accident-related keloid scar in 2005 intralesionally does not appear to have affected the patient's viral load negatively at that time.

A review of the literature found no other cases which could further clarify the situation [4] all available published experience of the interaction between ritonavir and triamcinolone resulting in IACS and secondary adrenal insufficiency, but a search of studies published in peer-reviewed journals were retrieved from the electronic databases Pubmed/Medline, EBSCOhost, CINAHL, PsycARTICLES, Google Scholar, and PsycINFO using the search terms enhanced protease inhibitors, Ritonavir, Cobicistat, and ICS produced no results.

What is characteristic of this case in the early stages area a) the generalised anxiety associated with observed consequences of HIV disclosure [5], and b) the preference of the patient's body to respond to HIV infection with an inflammatory immune response as opposed to an antibody response [6]. Despite activating coping mechanisms such as limiting disclosure to those who needed to know and restricting social activity to those who were also infected with HIV, the patient was unable to defend against the anxiety associated with the effect of generalised inflammation on his ability to carry out activities of everyday living including work. The bilateral Ulnar and Carpal Tunnel Syndrome, Achilles and Tibialis Posterior Tendinopathy and Plantar Faciopathy and the candidiasis and herpes simplex virus with associated persistent cough are all indicative of T-helper cell dysregulation and the B-cell depreciation resulting in an inflammatory rather than a humoral immune response. Although the introduction of the ART increased CD4⁺ T cell count and reduced the viral load, the ART also exacerbated the fatty liver, HSV, Hypertension, bilateral Ulnar and Carpal Tunnel Syndrome, Achilles and Tibialis Posterior Tendinopathy and Plantar Faciopathy.

The introduction of ePI following NNRTI failure gave rise to a series of symptoms that could best be described as an iatrogenic Cushing-like syndrome. Ritonavir, a potent inhibitor of the cytochrome P450 (CYP) 3A4 isoenzyme, is used to increase therapeutic levels of other PIs, (e.g., Lopinavir, Atazanavir, Darunavir), by preventing the reduction of the PI thus increasing PI bioavailability [7]. Unfortunately, in inhibiting the action of HMG CoA reductase, drugs like Ritonavir also increases the serum concentration of other drugs like Amlodipine used to treat hypertension, and cortisol released in response to inflammation and perceived stress [8]. Over the course of 3-4 months, the patient experienced uncontrollable increases in fat on face, arms, legs, abdomen back of the neck, hypertension, stretch marks, keloid scars, mood swings, and marked loss of libido), phlebotomy-associated keloid scars, erythematous gastritis and duodenitis, pedal and rectal oedema, and reduced anal sphincter complex tone and faecal incontinence with urinal frequency and urgency of unknown origin that could not be explained by a course of two intralesional Triamcinolone injections administered to keloid scars on the left forearm the following year. When these symptoms were raised with clinicians, they merely prescribed another combination of ePI presumably to secure adherence without consideration of the reported adverse effects of this combination.

For the patient, adherence to ART was not primarily biomedical aimed at stopping the spread of HIV [9]. The patient's concern, however, was primarily economic, (i.e., to be able to continue in his chosen career, and maintain a felt sense of well-being. Where the viral load becomes detectable after a period of being undetectable, clinicians invariably assumed that the patient has not taken medications as prescribed (times and frequencies)

and followed instructions regarding food and other medications without any evidence to support such assumptions. Failure to comply with ART for this patient seemed to be related more to the effect of the side effects on ART on his quality of life. Adhering to drug regimens often required a complete change in diet and dietary schedules, the prohibition of previously loved foods, adverse effects, and a significant reduction in freedom from which the patient could not escape nor avoid if he wanted to stay alive. No longer can the patient eat and drink when and what he likes, nor can he socialise where and with whom he likes. The patient always has to be on his guard for drug interactions, and people he meets within the context of his everyday life begin wondering why he is behaving the way he is and refusing to do things that previously he had done with thought willingly [10]. 'Information-Motivation-Behaviour', [11] 'Social Action Theory', and [12] 'Health Behavioural Model' go some way in explaining how information, social context, and perceptions and attitudes to HIV might influence ART adherence, but they fail to identify a causal relation between identified mechanism or variables/factors and adherence to medication and retention in care [13]. From this case study, it would appear that clinicians' primary concern of adherence to ART and retention in care is at odds with the patient's concern which is quality of life and a sense of wellbeing. The two outcomes do not appear to be related in this case study. Where the patient is at odds with clinicians, neither the clinician nor the patient is likely to will meet his or her desired outcomes. Factors such as poor experience of health care provider can be as detrimental to adherence as HIV stigma and discrimination [14]; However, unintended consequences of systemically ignoring the patient's report anxieties about his or her treatment and its effect can be traumatic. In failing to adjust the ART in response to the insurmountable objective evidence and patients reported concerns that something was wrong until the patient refused to take any more ePI ART, the health care providers gave the impression that adherence to ART was more important than the debilitating effect of the medication.

The literature identifies cases where a significant drug-drug interaction appears to have occurred between corticosteroid injections and combination therapy including enhanced protease inhibitors (ePI ART) for the treatment of HIV resulting in Cushing syndrome with adrenal insufficiency. In this case, however, the ePI ART seemed to result in a chronically raised serum cortisol which had the same effect. Both combinations involving Ritonavir and Cobicistat seemed to have the same effect and the Cushing symptoms and complete paralysis of the bowel seemed to be resolved when the patient was placed on ART that did not involve ePI. A search of the literature revealed no papers describing the onset of Cushing syndrome and adrenal insufficiency in isolation of corticosteroid therapy in patients taking ePI ART, however, understanding how serum cortisol may

mediate the relationship between ePI ART and viral load seems important if clinicians are to assess medication toxicities and maintain a good working relationship with patients. The case described illustrates the importance of clinical awareness of drug-drug interactions and the psychological impact of the symptoms on the patient cannot be underestimated when you considering adherence interventions. Chronic stress was a common theme within the context of this case study, and the relation between chronic stress and serum cortisol is well documented. Future research should attempt to examine the relationship between perceived stress and HIV viral load and determine how serum cortisol might mediate the relationship between psychological stress and viral load in patients taking ePI ART.

In this case, the course of action was to stop prescribing the enhanced protease inhibitors in response to the clinical reports from investigation into the patient's reported symptoms. Complaints of weight gain that does not respond to diet and excess, loss of power and flexibility in the hands, and general bloatedness should be followed by clinical tests for Cushing syndrome. Blood tests for raised serum cortisol can be done with tests for viral load, CD4 count, liver and kidney function. Clinicians should consider referral to endocrinology, hepatology, rheumatology and colorectal specialists at the earliest opportunity so that both the physician and the patient have all the information necessary to co-construct a health care plan and make clinical decisions going forward. Clearly patients will vary as to how much control over their health care they want and it is up to the clinicians to ascertain how involved in the care each patient wants to be. However, simply ignoring the patient is not an option if the aim is to encourage adherence and protect the public.

CONCLUSION

Enhanced protease inhibitors have proven an important course of treatment in the fight against HIV/AIDS, however, these very powerful drugs can have unintended consequences that are not very well documented. The reason for this is unclear. It is vitally important, however, that clinicians listen to and act on patients' concerns at the earliest opportunity to ensure adherence and attendance at clinic for the benefit of all concerned.

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Author Contributions

Vernon De Maynard – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

Guarantor of Submission

The corresponding author is the guarantor of submission.

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Consent Statement

Written informed consent was obtained from the patient for publication of this case report.

Conflict of Interest

Authors declare no conflict of interest.

Data Availability

All relevant data are within the paper and its Supporting Information files.

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