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Inhaled Corticosteroid Use in HIV-positive Individuals taking Protease Inhibitors: a Review of Pharmacokinetics, Case Reports, and Clinical Management

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Abstract

Due to the inhibition of hepatic cytochrome P450 3A4 isozyme, HIV protease inhibitors can result in significant drug-drug interactions. One noteworthy interaction is between protease inhibitors and inhaled or intranasal corticosteroids. This interaction can result in adrenal insufficiency, iatrogenic Cushing's syndrome (with symptoms such as rapid weight gain, obesity, facial hirsutism and swelling, etc.), as well as hypertension, osteoporosis, and decreased CD4+ cell count. In this paper, we review and unite pharmacokinetic data, case reports, and current research regarding this drug-drug interaction in order to provide options for the clinical management of HIV-positive patients requiring treatment with protease inhibitors and inhaled or intranasal corticosteroids.

Keywords

HIV; drug interactions; protease inhibitors; ritonavir; corticosteroid; pharmacokinetics

Introduction

Ritonavir is a potent inhibitor of the hepatic cytochrome P450 (CYP450) 3A4 isozyme and is used at low doses to boost the levels of other protease inhibitors (PIs) for the treatment of human immunodeficiency virus (HIV).⁽¹⁾ Due to this property, the use of ritonavir and other PIs can result in numerous drug-drug interactions. Inhaled and intranasal corticosteroids, such as beclomethasone, budesonide, ciclesonide, flunisolide, fluticasone, mometasone, and triamcinolone, are mostly substrates of hepatic CYP3A4 and have the potential to interact with ritonavir. These interactions can result in steroid accumulation, adrenal suppression, and Cushing's syndrome. Given the widespread use of intranasal and inhaled corticosteroids for allergic rhinitis, asthma, and chronic obstructive pulmonary disease, there is a potential for the erroneous prescription and use of these medications in HIV-positive adult and

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pediatric patients on a PI-containing antiretroviral regimen. The purpose of this article is to review the literature on the pharmacokinetics of inhaled and intranasal corticosteroids and case reports regarding this drug-drug interaction and to provide options for the clinical management of HIV-positive patients requiring treatment with PIs and inhaled or intranasal corticosteroids.

Pharmacokinetics of corticosteroid inhalers

In the absence of sufficient drug-drug interaction studies between inhaled/intranasal corticosteroids and PIs, attention to key pharmacokinetic properties may help us elucidate which agents may be safer to use when the combination of these two classes are necessary. The extent of the corticosteroid metabolism by CYP3A4 isozyme is a critical factor in determining whether it will be affected by PIs and other CYP3A4 inhibitors. Other important properties that may minimize this drug-drug interaction include: 1) less systemic exposure as measured by glucocorticosteroid relative receptor binding affinity (RRA), which can translate to decreased nasal passage and lung receptor binding and decreased potency; 2) lower systemic oral bioavailability (F), which is the extent to which the drug reaches the blood and can result in systemic side effects; 3) higher plasma protein binding (Pb), which results in lower fraction unbound and prevents the drug's diffusion into the tissue; and 4) shorter elimination half-life, which is determined by the volume of distribution and clearance of the drug; 5) lower lipophilicity, which translates to lower distribution and binding of the drug to the tissue.(2)

In Table 1 we have summarized and compared pertinent characteristics of inhaled/intranasal corticosteroids in order to detect those that may have a low risk of interaction and adverse effects. Among the available inhaled/intranasal corticosteroids, flunisolide and beclomethasone seem to meet most of the properties mentioned above, such as low RRA, low lipophilicity, short elimination half-life, and less dependence on metabolism by CYP3A4 isozyme. Fluticasone exhibits the most suppressive impact on the hypothalamic-pituitary-adrenal axis.(3) This is likely due to its pharmacokinetic properties, such as higher lipophilicity, longer elimination half-life, prolonged glucocorticoid RRA, as well as its relatively exclusive metabolism by CYP3A4.(4–7)

Case reports of the corticosteroid-protease inhibitor drug-drug interaction

Through searching PubMed, references of pertinent articles, and contact with respective drug companies, we identified 51 case reports published in English regarding adverse effects with the use of inhaled (n=45), intranasal (n=2), and combination inhaled and intranasal (n=4) corticosteroids and PIs (Table 2).(8–32) Papers were published between the years 1999 and 2012. There were 9 (18%) reported cases in the pediatric population (i.e., <12 years of age),(8–11) 19 (37%) cases in women,(8–10, 12–17, 21, 28) and the mean age of patients was 36 years (range=1.8–66 years). Ritonavir was part of the antiretroviral regimen in 48 (94%) of the cases, other PIs (indinavir, saquinavir, and nelfinavir) in 2 (4%) of cases, (26, 27) and the antiretroviral regimen was not reported in one case (2%)(9). The mean daily dose of ritonavir in pediatric cases was 109mg/day and the mean dose in adult cases was 224mg/day (range=100–1200mg/day). Among the 45 cases of inhaled corticosteroid alone, 91% used fluticasone(8–10, 12–14, 16, 17, 20–26, 29, 31, 32) and 9% used budesonide(9, 26–28). Fluticasone was used in both cases of intranasal corticosteroid(18, 19). Four cases of combined inhaled and intranasal corticosteroids consisted of budesonide inhaled and intranasal(9), fluticasone inhaled and mometasone intranasal(11), beclomethasone inhaled and fluticasone nasal(19), and fluticasone inhaled and intranasal(30). The mean daily dose of inhaled fluticasone in the pediatric population was 343µg/day (range=50–1000µg/day) and in adults, the mean inhaled dose was approximately 841µg/day (range=200–2000µg/

day). The mean daily dose of intranasal fluticasone was 400µg/day (range=200–800µg/day), which were all in adult patients.

As a point of reference, the recommended maximum daily doses of inhaled fluticasone propionate aerosol inhalation and oral powder inhalation for pediatrics are 176µg/day or 200µg/day, respectively. The maximum daily dose of fluticasone propionate aerosol inhalation for adults is 880µg/day and 2000µg/day for oral powder inhalation. The total recommended daily doses of intranasal fluticasone furoate and fluticasone propionate in adults are 110µg/day and 200µg/day, respectively. Therefore, the mean doses used in both the pediatric and intranasal adult cases were substantially higher in comparison to the recommended maximum daily doses of fluticasone; however, the inhaled doses in the adult case reports were within the recommended daily dose range.

The duration of corticosteroid-PI co-administration prior to onset of symptoms was highly variable, ranging from ten days to five years (mean=7.1 months). Symptoms reported also varied, although the most common were typical symptoms associated with Cushing's syndrome including facial swelling (also known as "cushingoid facies" or "moon face"), facial hirsutism, central obesity and weight gain, dorsocervical fat pad (also known as "buffalo hump"), striae, and easy bruising. A reduction in CD4+ cell count and oropharyngeal candidiasis was reported in several studies.(20, 25, 26, 31, 32) Adverse effects seemed to be more severe in those 60 years of age and included osteonecrosis of hips, vertebral and femoral fractures, and severe hypertension.

Common methods of clinical management which resulted in the resolution of symptoms consisted of either tapering and eventually discontinuing the inhaled/intranasal corticosteroid, discontinuation of the inhaled/intranasal corticosteroid and initiation of a slow taper of oral corticosteroid, or changing the PI-based regimen to a non-nucleoside reverse transcriptase inhibitor-based regimen. Among 43 cases with reported outcome, 95% had resolution of symptoms and normalization of cortisol or adrenocorticotrophic hormone (ACTH) levels within a mean of 12.1 weeks (range =2–24 weeks) and 10.1 weeks (range =3–24 weeks), respectively.

Considerations for clinical management, options for treatment, and future research

It is critical to collect a thorough medication history in patients exhibiting signs and symptoms of Cushing's syndrome. Additionally, it is important to distinguish between lipodystrophy, caused by some antiretroviral medications, and iatrogenic Cushing's syndrome, as they have many overlapping characteristics (e.g., central obesity, weight gain, and dorsocervical fat pad).(33) However, abdominal striae, easy bruising, facial plethora, rapid weight gain, increased appetite, and facial hirsutism are commonly related to Cushing's syndrome and peripheral atrophy is more likely to be noted in lipodystrophy. For the diagnosis of adrenal insufficiency, an early morning plasma cortisol level should be obtained followed by the 30-minute synthetic adrenocorticotrophic hormone (ACTH) or cosyntropin stimulation test. A cortisol level >11 µg/dL is unlikely to be associated with significant adrenal insufficiency; however, levels <3 µg/dL are strongly suggestive of adrenal insufficiency. A decreased response to the ACTH stimulation test is diagnostic of adrenal insufficiency.

Due to the staggering number of case reports, a prior literature review by Foisy and colleagues clearly advises against the co-administration of fluticasone with ritonavir(34). However, despite the presence of these well-documented cases and the fact that electronic prescribing systems generally provide warnings against the combination of most PIs and

some corticosteroids (e.g., fluticasone, mometasone, and budesonide), patients continue to inadvertently receive these medications. Most importantly, there is little guidance and recommendations for the medical management of patients requiring treatment for HIV and asthma or allergic rhinitis. From our review, possible options include: 1) initiating or changing the PI to another antiretroviral agent that does not inhibit the CYP3A4 isozyme (such as non-nucleoside reverse transcriptase inhibitors or integrase inhibitors), if this is allowable based on the drug resistance and treatment history; 2) substituting the inhaled/intranasal corticosteroid with another corticosteroid with less potential for drug interactions (we will discuss these options below); or 3) using an alternative medication, such as a leukotriene receptor antagonist (e.g., montelukast), a mast cell stabilizer (e.g., cromolyn), anticholinergic agent (e.g., ipratropium), or an antihistamine. It is unclear if significant dose reductions in the inhaled/intranasal corticosteroid dose will result in complete resolution or avoidance of this drug-drug interaction(31) and there are case reports with inhaled fluticasone dose as low as 200 µg/day(8, 13). Those diagnosed with Cushing's syndrome should be evaluated for potential need to initiate oral steroid replacement and gradual taper(35) being careful to reduce the steroid dose if the PI is continued(36). Adrenal function recovery may take 9–12 months(35, 37) and serum cortisol levels can be checked every 4–6 weeks(35) to reassess the need for ongoing steroid replacement therapy.

It is noteworthy that this drug-drug interaction is not limited to inhaled and intranasal corticosteroids. Cushing's syndrome has been previously reported when injectable(38, 39) and topical corticosteroids(40, 41) were used in conjunction with CYP3A4 inhibitors. In a recent cohort study, the prevalence of iatrogenic Cushing's syndrome in HIV-positive individuals receiving a ritonavir-containing antiretroviral regimen in addition to inhaled, intranasal, or topical corticosteroids (for 1 month and using 4.5% of total body surface area) was examined.(42) Approximately 35% of individuals met the diagnosis criteria of Iatrogenic Cushing's syndrome, including one patient using topical triamcinolone. The injection of triamcinolone in patients on ritonavir has similarly resulted in the development of Cushing's syndrome(38, 39). Therefore, this is a potential risk for all individuals on PIs who are chronically using corticosteroids via any route.

One of the few studies to specifically evaluate the drug-drug interaction between corticosteroids and PIs was recently presented.(43, 44) This was a randomized open-label study in HIV-negative healthy adults. The investigators evaluated whether ritonavir alone or darunavir/ritonavir could significantly increase plasma concentrations of beclomethasone 17-monopropionate (17-BMP), the more active metabolite of beclomethasone dipropionate (BDP).(43) Additionally, they investigated whether inhaled BDP when co-administered with ritonavir or darunavir/ritonavir could significantly influence adrenal function in these participants.(44) For 14 days, 30 subjects received orally inhaled BDP 160 µg twice daily and on day 15, they were randomized (1:1:1) to three groups: Group 1 (control) remained on BDP alone for 14 days; Group 2 received BDP and ritonavir (100mg twice daily) for 14 days; and Group 3 received BDP and darunavir/ritonavir (600/100mg twice daily) for 14 days. It was noted that darunavir/ritonavir did not significantly increase the area under the concentration-time curve of 17-BMP and did not cause significant adrenal suppression. Ritonavir alone resulted in a two-fold increase in 17-BMP, which was statistically significant; however, given that this increase did not result in significant adrenal suppression, it was not considered clinically consequential. The authors concluded that the use of BDP is preferable to fluticasone in patients receiving a PI and requiring an inhaled corticosteroid. Given the fact that PIs exhibit varying degrees of CYP3A4 inhibition, these promising results with the use of BDP should be used with caution and warrants further research.

Until additional research in this area, we can gain some reassurance that based on pooled pharmacokinetic data (Table 1), cases reports (Table 2), and prior research(43, 44), inhaled or intranasal beclomethasone is a relatively safe options in HIV-positive individuals who are receiving PIs. Additionally, based on the pharmacokinetic comparison of these compounds (Table 1), flunisolide appears to have low risk of drug-drug interaction and may be another potential option due to its similarly low glucocorticoid RRA, low lipophilicity, short elimination half-life, and its insubstantial CYP3A4 metabolism.

The drug-drug interaction between corticosteroids, especially fluticasone, and PIs is significant and deserves close attention and evaluation. Physicians, pharmacists, and other health care providers should be further educated on the risks associated with this drug-drug interaction and be provided with alternative options for the treatment and resources for the management of patients. Electronic prescribing systems should frequently be updated to ensure accuracy of warnings for the use of corticosteroids via any route and PIs. Pharmacists should regularly generate lists of patients who may have inadvertently received inhaled/ intranasal corticosteroids and PIs and advise prescribing clinicians of appropriate substitutions. Lastly, future research should examine the use of inhaled/intranasal corticosteroids, such as beclomethasone and flunisolide, in HIV-positive individuals receiving commonly prescribed PIs.

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Table 1

Pharmacokinetic properties of inhaled/intranasal corticosteroids

	17-BMP (ref.)	BDP	BUD	CIC	FLU	FF	FP	MF	TAA
RRA ¹	1345 (44)	43 (44)	855 (45)	1212 (Des-CIC) (2)	180 (2)	2990 (46)	1910 (5)	2200 (47)	233 (2)
Lipophilicity ²	ND	1.3 (48)	1.9 (48)	4.08–5.32 (48)	1.1 (48)	ND	3.4–3.46 (7, 48)	2.1–3.49 (7, 48)	0.2 (48)
Half-life, hour ³	2.7 (49)	0.5 (49)	2–3 (50–52)	0.36 (53)	1–2 (54)	15.3 (55)	7.8(56)	5 (57, 58)	3.6 (59)
Pb, %	94–96 (60)	87 (44, 61)	85–90 (51, 52)	99 (53)	80 (54)	99.4 (62)	99 (56)	98–99 (57, 58)	68–71 (63, 64)
Metabolism	ND	Esterase & 3A4 (44, 60, 65)	3A4 (51, 52)	CIC: esterase Des-CIC: 3A4, 2D6 (53)	Glucuronidation, sulfation (54)	3A4 (62)	3A4 (56)	P450 3A4 (57, 58)	6 β -hydroxylation (63, 64)
F_{oral}, %	41 (49)	~0 (49)	10 (51)	<1 (53)	20 (54)	1.26 (62)	<1 (56)	<0.1 (57, 58)	23 (63, 64)

17-BMP: 17-beclomethasone monoproprionate (active metabolite of BDP); BDP: beclomethasone dipropionate (inhaled: QVAR, Beclovent; nasal: Beconase, Qnasl); BUD: budesonide (inhaled: Pulmicort, Symbicort (co-formulated with formoterol); nasal: Rhinocort); CIC: ciclesonide (inhaled: Alvesco; nasal: Omnis, Zetonna); Des-CIC: des-ciclesonide (active metabolite of CIC); Foral: systemic bioavailability; FF: fluticasone furoate (nasal: Veramyst); FP: fluticasone propionate (inhaled: Flovent, Advair (co-formulated with salmeterol); nasal: Flonase, Dymista (co-formulated with azelastine)); FLU: flunisolide (inhaled: Aerobid; nasal: Nasalide); MF: mometasone furoate (inhaled: Asmanex, Dulera (co-formulated with formoterol); nasal: Nasonex); ND: no data; Pb: protein binding; RRA: relative receptor affinity; TAA: triamcinolone acetonide (inhaled: Azmacort; nasal: Nasacort AQ)

¹With dexamethasone as reference (RRA = 100)

²Based on logarithm of octanol to water partition coefficient

³Half-life reported as elimination half-life (half-life with intravenous administration) with exception of BUD and TAA, which were reported as terminal half-life (half-life with oral or nasal administration).

Table 2

Case reports of inhaled/intranasal corticosteroid-protease inhibitor drug-drug interaction

Case number (ref.)	Year	Age Sex	ART	RTV total daily dose	Other medications	Corticosteroid type Inhaled / Nasal Daily dose (µg)	Duration of co-admin before onset	Signs & Symptoms	Management	Outcome
1 (8)	2006	1.8 years Female	LPV/RTV, ddT, 3TC	60mg	TAA ointment	FP Inhaled 220	6.2 months [*]	Weight gain, ACTH & cortisol suppression	FP taper off	Resolution of cortisol 4 months after taper; repeated cortisol & ACTH due to TAA ointment
2 (9)	2010	4 years Female	RTV- Containing regimen	300mg/m ²	NR	BUD Inhaled & nasal 1200	3 months	Facial lipohypertrophy, truncal obesity, facial hirsutism	BUD to 200µg x1 week morning cortisol <1 mmol/L; d/c BUD 1 week later	Morning cortisol was 222mmol/L 3 weeks later
3 (9)	2010	4 years Female	LPV/RTV- containing egimen	235mg/m ²	NR	BUD Inhaled 200	2 years	Facial & truncal obesity, facial hirsutism, dorsocervical fat pad	Switch LPV/RTV to EFV	Morning cortisol from 8 to 278 mmol/L after 4 weeks
4 (9)	2010	7 years Male	NR	NR	Salmeterol	FP Inhaled 50	2 months	Facial & truncal obesity, dorsocervical fat pad, facial hirsutism	FP changed to BUD; no change; d/c BUD	Morning cortisol from 5 to 115 mmol/L after 6 weeks
5 (10)	2009	9 years Female	LPV/RTV, ABC, ddl	NR	NR	FP Inhaled 250	NR	Cushing's syndrome	NR	NR
6 (11)	2007	9 years Male	LPV/RTV, ddl, 3TC	108mg	Montelukast	FP Inhaled 440 & MF Nasal 100	FP: 2 months MF: 11 months	Cushingoid facies, facial irsutism, weight gain	Taper & d/c FP & MF over 4 weeks	Resolution of symptoms 2 weeks after completion of taper
7 (8)	2006	9.5 years Male	LPV/RTV, 3TC, TDF	133mg	NR	FP Inhaled 220	6.2 months [*]	Cushing's syndrome	d/c FP; initiate prednisone taper	Resolution of symptoms within 3 months
8 (10)	2009	10 years Female	LPV/RTV, ABC	NR	Topical BDP	FP Inhaled 1000	NR	Cushing's syndrome	NR	NR
9 (8)	2006	11.4 years Female	LPV/RTV, ddT, 3TC	133mg	NR	FP Inhaled 220	6.2 months [*]	Cushing's syndrome	d/c ART & FP; initiate EFV, ddl, FTC	Resolution of symptoms within 3 months
10 (12)	2006	12 years Female	3TC, ZDV, LPV/RTV	134mg	Salmeterol Albuterol Montelukast Fluconazole Azithromycin Co-trimoxazole Dexamethasone (IV x13 days)	FP Inhaled 500–1000	60 days	Weight gain, abdominal girth, striae, hirsutism, nausea, vomiting, diarrhea, poor appetite, epigastric pain, easy bruising, livedo reticularis, malaise	Change LPV/RTV to EFV	Hospitalization for adrenal suppression & Cushing's; cortisol & ACTH normalized 6 months after LPV/RTV d/c

Case number (ref.)	Year	Age Sex	ART	RTV total daily dose	Other medications	Corticosteroid type Inhaled / Nasal Daily dose (µg)	Duration of co-admin before onset	Signs & Symptoms	Management	Outcome
11 (13)	2011	12 years Female	ZDV, 3TC, LPV/RTV	200mg	NR	FP Inhaled 200	24 weeks	Fatigue, weight gain, cushingoid facies, rash, insulin resistance	Taper FP & d/c & start Montelukast	Resolution of symptoms, cortisol, ACTH, & insulin levels 3 months after FP d/c
12 (14)	2007	14 years Female	ddI, TDF, ATV, RTV	100mg	Salmeterol Motelukast	FP Inhaled 500	2 weeks	Weight gain, striae, cushingoid facies, facial hirsutism,	d/c ATV, RTV, & FP; hospitalization for adrenal insufficiency; HCT x2 weeks	Resolution
13 (12)	2006	15 years Female	3TC, ABC, LPV/RTV	200mg	Salmeterol Prednisone (x10 days)	FP Inhaled 1000	13 weeks	Weight gain, cushingoid facies, striae, hirsutism, central adiposity	FP to 500µg & then 200µg	Normalized cortisol level & ceased weight gain 2 months after FP
14 (10)	2009	16 years Male	Fos-APV, RTV, ZDV, TDF	NR	NR	FP Inhaled 500	NR	Cushing's syndrome	NR	NR
15 (15)	2007	16 years Female	3TC, ddT, RTV	NR	Salmeterol	FP Inhaled 500	3 months	Weight gain, acne, striae, amenorrhea, fatigue, facial edema, hypercholesterolemia, amenorrhea, appetite	Change RTV to EFV	Resolution of symptoms in 30–60 days; normalized cortisol in 5 months
16 (8)	2006	16.8 years Male	LPV/RTV, ABC, AZT, 3TC	200mg	NR	FP Inhaled 250	6.2 months *	Cushing's syndrome	d/c all medications	Resolution within 3 months
17 (8)	2006	20.9 years Male	ATV, RTV, ddI, TDF	100mg	NR	FP Inhaled 200	6.2 months *	Cushing's syndrome	d/c FP	Resolution within 3 months
18 (16)	2005	27 years Female	LPV/RTV, SQV	200mg	Salmeterol Methadone Benzodiazepine	FP Inhaled 1000	10 weeks	Weight gain, myopathy, central adiposity, striae, dorsocervical fat pad	d/c FP; initiate oral steroids	Resolution
19 (17)	2009	29 years Female	ATV, RTV - containing regimen	NR (presumably 100mg)	NR	FP Inhaled 2000	1 month	Weight gain, facial plethora, severe myalgias, amenorrhea	Change ATV/ RTV to NVP-containing regimen	Resolution in 3 months; adverse effects seen with ATV/RTV rechallenge; FP d/c; symptom resolution in 3 months
20 (18)	1999	30 years Male	RTV, ZDV, 3TC	1200mg	Cutaneous corticosteroid preparation	FP Nasal 200	6 months	Cushingoid facies, adrenal failure	Change RTV to NVP	Resolution; adverse effect seen with RTV rechallenge
21 (10)	2009	31 years Female	LPV/RTV, 3TC, TDF	NR (presumably 200mg)	NR	FP Inhaled 1000	NR	Cushing's syndrome	NR	NR
22 (19)	1999	32 years Male	RTV, ZDV, 3TC	NR	NR	FP Nasal 400	5 months	Weight gain, cushingoid facies	d/c FP	Resolution of adrenal function & morphologic changes in 5 weeks

Case number (ref.)	Year	Age Sex	ART	RTV total daily dose	Other medications	Corticosteroid type Inhaled / Nasal Daily dose (µg)	Duration of co-admin before onset	Signs & Symptoms	Management	Outcome
23 (20)	2002	33 years Male	d4T, 3TC, APV, RTV	200mg	Terbutaline, Salmeterol	FP Inhaled 1000	5 months	Cushingoid facies, weight gain, acne, candida esophagitis	d/c FP	Resolution of clinical symptoms in 2 months
24 (21)	2010	37 years Female	TDF, FTC, LPV/RTV	200mg	Salmeterol	FP Inhaled 250	4–7 months	Weight gain, hyperpigmentation, mild edema of shins, striae, HTN	d/c FP	Resolution of symptoms in 2 months; symptoms reoccurred in 4 weeks with BUD (320µg/day) & did not resolve with RTV 100mg; resolution in weeks after d/c of BUD & start montelukast
25 (22)	2004	38 years Male	LPV/RTV, 3TC, d4T	NR (presumably 200mg)	NR	FP Inhaled 2000	10 days	Cushingoid facies, appetite	d/c FP & start BDP	Resolution of symptoms & cortisol level in 3 weeks (adverse effect seen with FP rechallenge)
26 (19)	1999	39 years Male	SQV, RTV, d4TC, NVP	NR	NR	BDP Inhaled 400–800 & FP Nasal 800	18 months	Mild cushingoid facies	d/c FP	NR
27 (10)	2009	42 years Male	LPV/RTV, 3TC, d4T	NR (presumably 200mg)	NR	FP Inhaled 2000	NR	Cushing’s syndrome	NR	NR
28 (23)	2005	43 years Male	LPV/RTV, APV, ddl	200mg	NR	FP Inhaled 500	2 years	Rib fractures, central weight gain, striae, facial plethora, acne, dorsocervical fat pads, appetite, weakness, bruising, irritability, depression	d/c FP, hypocortisolism prompted initiation of oral prednisolone taper	Resolution of dorsocervical fat pads & facial plethora in 5 months
29 (23)	2005	43 years Male	RTV, ZDV, NVP	100mg	Ketoconazole	FP Inhaled 500	1–2 months	Facial rash, truncal & abdominal fat, facial plethora, muscle wasting, depression; severe lumbar osteoporosis	d/c FP; hypocortisolism prompted initiation of oral prednisolone taper	Resolution of cortisol level 6 months later
30 (23)	2005	43 years Male	LPV/RTV, ABC	200mg	NR	FP Inhaled 500	6 weeks	Severe muscle cramping, abdominal obesity, facial plethora, bruising	d/c FP; initiate low-dose oral prednisolone	Clinical features evident 2 months later
31 (24)	2003	44 years Male	ABC, ddl, LPV/RTV	266.4mg	NR	FP Inhaled 2000	2 months	Weight gain, facial & truncal Obesity, striae	Change FP to montelukast	Resolution of symptoms in 1 month
32 (25)	2002	45 years Male	EFV, SQV, RTV	800mg	Albuterol, Prednisone (x5 days)	FP Inhaled 880	20 days	Weight gain, CD4+, dorsocervical fat pad, istended abdomen, striae	Slow taper & d/c of FP over 3 months	Resolution of symptoms & CD4+ over 5 months

Case number (ref.)	Year	Age Sex	ART	RTV total daily dose	Other medications	Corticosteroid type Inhaled / Nasal Daily dose (µg)	Duration of co-admin before onset	Signs & Symptoms	Management	Outcome
33 (26)	2012	45 years Male	ATV, RTV, ABC, 3TC, TDF	NR (presumably 100mg)	Formoterol	BUD Inhaled 160	2 months	Low morning cortisol & low- normal ACTH	d/c BUD & initiate montelukast	Normalized cortisol level in 2 months
34 (27)	2001	47 years Male	ZDV, ddI; then ddT, ddI, IDV	NA	Oral steroids (3 courses x7 days)	BUD Inhaled 1600–3200	6 months	Abdominal distension, muscle weakness & pain, Cushingoid features	IDV changed to NVP; d/c BUD	Resolution with d/c of BUD
35 (26)	2012	48 years Male	ZDV, 3TC, LPV/RTV	NR (presumably 200mg)	Fluconazole, Omeprazole, Cortimoxazole, Salmeterol	FP Inhaled 1000	4 weeks	Hoarseness, facial edema, weight gain, parotid swelling	d/c FP	Normalized cortisol & ACTH after 4 weeks; gradual resolution of symptoms
36 (28)	2012	48 years Female	DRV, RTV, FTC, EFV	NR	Formoterol Montelukast	BUD Inhaled 1600	18 months	Worsening of Cushingoid appearance (weight gain, truncal obesity, striae, dorsocervical fat pad)	Reduce BUD dose to 800 µg/day & d/c; change DRV/ RTV to RAL	Normalized cortisol level; unchanged Cushingoid features that may have been due to lipohypertrophy
37 (23)	2005	49 years Male	RTV, SQV, ZDV, 3TC	200mg	Salmeterol, prednisolone (x10 days)	FP Inhaled 1000	NR (<6 weeks)	Abdominal distension, facial plethora, presyncope, HTN, fatigue, osteoporosis	Changed RTV & SQV to EFV; hypocortisolism prompted initiation of oral prednisolone taper	Resolution of physical symptoms over few months
38 (23)	2005	51 years Male	LPV/RTV- then RTV- containing regimen	200mg; then 100mg	Gliperimide Rosiglitazone	FP Inhaled 1000	2 months	glucose levels, muscle cramps, weakness, wasting, mood changes, abdominal bloating, facial plethora	d/c FP	Resolution of clinical features by 4 months
39 (29)	2012	52 years Male	RTV- containing regimen	NR	Salmeterol	FP Inhaled 500	5 years	Vertebral fracture & deformities, osteoporosis, hypogonadism	Taper FP	NR
40 (32)	2012	52 years Male	RTV, ATV, EFV	NR (presumably 100mg)	Fluconazole	FP Inhaled 500–1000	>2 months	Fatigue, weakness, cramping, mouth sores, hoarseness, oropharyngeal candidiasis, blood glucose, CD4+	D/c FP, initiate HCT replacement	Resolution of symptoms in several weeks; CD4+ increased in 1–2 months
41 (23)	2005	53 years Male	LPV/RTV, ABC, NVP	200mg	Rosiglitazone	FP Inhaled 1000	Shortly after	Facial plethora, bruising, osteopenia	d/c FP	Resolution of symptoms after 4 months
42 (13)	2011	55 years Female	ZDV, 3TC, LPV/RTV	200mg	Salmeterol	FP Inhaled 1000	3 weeks	Fatigue, weight gain, cushingoid facies	Taper FP & d/c & replace with BUD (400 µg/day)	Resolution of symptoms after 3 months

Case number (ref.)	Year	Age Sex	ART	RTV total daily dose	Other medications	Corticosteroid type Inhaled / Nasal Daily dose (µg)	Duration of co-admin before onset	Signs & Symptoms	Management	Outcome
43 (30)	2011	60 years Male	RTV, ATV, ZDV, 3TC, TDF	NR (presumably 100mg)	Albuterol, Salmeterol	FP Inhaled 1000 FP Nasal 200	Inhaled: 2 months Nasal: 3.2 years	Vertebral fracture, femoral fracture, osteonecrosis of both hips, central obesity muscular atrophy in extremities	Taper FP & start HCT	Total hip replacement therapy
44 (26)	2012	60 years Male	SQV, 3TC, FV, ZDV	NA	Salmeterol	FP Inhaled 1000	1.5 years	Gynecomastia, facial edema, relapsing anal HSV, diarrhea	Change ART to ATV, RTV, 3TC, TDF; developed cellulitis, weakness, edema, weight gain, cushingoid face, parotid swelling, CD4+ 8 weeks later; d/c ART	Resolution of symptoms after 3 months; serum cortisol with restart of NFV; FP changed to BUD (160µ) with resolution of cortisol level
45 (29)	2012	60 years Male	RTV- containing regimen	NR	Salmeterol	FP Inhaled 500	12 months	Central obesity, cushingoid facies, HTN, muscle weakness dorsocervical fat pad, weight	d/c FP; initiate oral prednisolone taper	Resolution of symptoms
46 (17)	2009	65 years Female	LPV/RTV – containing regimen	NR (presumably 200mg)	NR	FP Inhaled 500	6 months	Weight gain, cushingoid facies, abdominal, neck, & face fat, myopathy, acne, striae, severe osteoporosis	d/c FP; initiate low dose HCT	Resolution of morphologic changes in 6 months
47 (13)	2011	65 years Female	ZDV, 3TC, LPV/RTV	200mg	Salmeterol	FP Inhaled 500	6 months	Weight gain, fatigue, facial swelling	Tape & d/c FP	Resolution 2–3 months after d/c FP
48 (31)	2005	66 years Male	ZDV, 3TC, IDV, RTV	200mg	Salmeterol Prednisolone (oral; 5 courses over 12 months)	FP Inhaled 1000	12 months	Bilateral foot drop, fatigue, concentration, memory loss, easy bruising, central obesity, esophageal candidiasis	FP dose by half	NR
49 (31)	2005	66 years Male	ddI, d4T, APV, RTV, ABC	200mg	Salmeterol	FP Inhaled 1000	6 months	Bilateral leg pain, weight gain in face & abdomen, thinning of skin, muscle weakness, oral candidiasis, cushingoid facies	Change FP to BUD (800µg/day) & cortisone	Resolution in 6–12 months; later developed fracture of right neck of femur & avascular necrosis
50 (17)	2009	66 years Male	ATV, RTV- containing regimen	NR (presumably 100mg)	NR	FP Inhaled 500	1–3 month	Vertebral pain, faciotroncular obesity, dorsocervical fat pad,	d/c FP; initiate oral HCT	Resolution after 5 months

Case number (ref.)	Year	Age Sex	ART	RTV total daily dose	Other medications	Corticosteroid type Inhaled / Nasal Daily dose (µg)	Duration of co-admin before onset	Signs & Symptoms	Management	Outcome
51 (17)	2009	66 years Male	LPV/RTV- containing regimen	NR (presumably 200mg)	NR	FP Inhaled 500	3–12 months	myopathy, depression, HTN Severe HTN, diabetes, myopathy, easy bruising, hypertriglyceridemia, hyperlactatemia, obesity	d/c ART; resolution of lactate in 3 weeks; restart RTV; develop KS & osteoporosis; d/c FP after 2 years; start HCT	Normalized cortisol & ACTH in 1 month; resolution of symptoms after 5 months

3TC: lamivudine, ABC: abacavir, ACTH: adrenocorticotrophic hormone; AMP: amprenavir, ART: antiretroviral therapy; ATV: atazanavir; BDP: beclomethasone dipropionate; BUD: Budesonide; d/c: discontinue; d4T: stavudine; ddl: didanosine; DRV: darunavir; EFV: efavirenz; Fos-APV: fos-amprenavir; FP: fluticasone propionate; FTC: emtricitabine; HCT: hydrocortisone; HSV: Herpes Simplex virus; HTN: hypertension; ICS: inhaled corticosteroid; IDV: indinavir; KS: Kaposi’ s sarcoma; LPV/RTV: lopinavir/ritonavir; MF: mometasone furoate; NA: not applicable; NFV: nelfinavir; NR: not reported; NVP: nevirapine; RAL: raltegravir; RTV: ritonavir; SQV: saquinavir; TDF: tenofovir; TAA: triamcinolone acetonide; ZDV: zidovudine

* Case series reported as mean duration of co-administration