Published in final edited form as:

J Acquir Immune Defic Syndr. 2013 August 15; 63(5): 602–608. doi:10.1097/QAI.0b013e31829b662b.

High frequency of hypothalamic-pituitary-adrenal axis dysfunction after local corticosteroid injection in HIV-infected patients on protease inhibitor therapy

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Abstract

Background—The frequency of hypothalamic-pituitary-adrenal (HPA) axis dysfunction among HIV-infected patients receiving steroid injections has not been reported, and risk factors for this adverse event are poorly characterized.

Methods—We conducted a retrospective analysis of data from HIV-infected patients in the Partners HealthCare system (Boston, MA) who received corticosteroid injection(s) between 2002 and 2011. Chart review focused on HIV status, antiretroviral therapy (e.g., protease inhibitors (PI)), steroid injection(s), and adrenal axis dysfunction (e.g., adrenal insufficiency (AI) and/or Cushing's syndrome). Because all cases occurred among patients on PIs, we performed additional detailed data extraction and conducted univariate and multivariate analyses to identify risk factors in this group.

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Potential Conflicts of Interest: RTG has received grant support from Tibotec (now Janssen), Abbott and Viiv.

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Results—171 HIV-infected patients received 1 corticosteroid injection(s) in the study period. Nine cases (event frequency, 5.3%; 95% CI, 2.4%-9.8%) of secondary AI were diagnosed; five (55%) of these nine patients also had clinical evidence of Cushing's syndrome. All cases occurred among the 81 patients on PIs (event frequency among those on PIs, 11.1%; 95% CI, 5.2%-20.0%). Among patients on PIs, the major risk factor for HPA-axis dysfunction was having 2 injections within 6 months.

Conclusions—In this retrospective cohort study, 11% of HIV-infected patients on PIs at the time of steroid injection were later diagnosed with HPA axis dysfunction. Corticosteroid injections in HIV-infected patients on PIs should only be used with great caution and close monitoring.

Keywords

HIV; adrenal insufficiency; Cushing's syndrome; corticosteroid; protease inhibitor; CYP3A4

Introduction

As HIV-infected patients live longer on effective antiretroviral therapy (ART),^{1, 2} the management of comorbidities is a growing challenge. To treat other disorders, many HIV-infected patients receive additional medications, some of which interact with antiretroviral agents. For instance, HIV protease inhibitors (PI) interact with corticosteroids by inhibiting the CYP3A4 pathway,^{3, 4} which can reduce the breakdown of exogenous steroids and result in elevated systemic steroid levels; this effect can lead to hypothalamic-pituitary-adrenal (HPA) axis dysfunction, including Cushing's syndrome, with or without secondary adrenal insufficiency (AI). The interaction between PIs and steroids is particularly important because a growing number of HIV-infected patients are developing problems seen in an aging population, such as osteoarthritis and musculoskeletal complaints, for which corticosteroid injections offer therapeutic relief.^{5, 6}

Case reports have highlighted the development of Cushing's syndrome and AI in the setting of intra-articular corticosteroid injections.⁷⁻¹¹ However, to our knowledge, the frequency of and risk factors for HPA-axis dysfunction in HIV-infected patients has not yet been studied systematically. We conducted a retrospective cohort study to assess the frequency of HPA-axis dysfunction in HIV-infected patients who receive one or more corticosteroid injections and to describe risk factors and outcomes.

Methods

Study Population

Patients were eligible for inclusion in the study population if, between January 2002 and October 2011, they were >18 years old, HIV-infected, and had a corticosteroid injection to any joint, trigger point, or nerve block at Massachusetts General Hospital, Brigham and Women's Hospital, or other clinical institution affiliated with the Partners HealthCare System in Boston, Massachusetts.

A two-stage strategy was used to identify the study cohort. We first identified potential subjects using the Partners Healthcare System Research Patient Data Registry (RPDR), which is an electronic data registry of all billed inpatient and outpatient encounters. This registry can be used to identify patients with specific diagnoses, laboratory tests, and/or procedures. We used the RPDR Query Tool to identify patients with International Classification of Diseases, Ninth Revision (ICD-9) diagnosis codes indicating HIV infection (codes 042, 043, and v08) and Current Procedural Terminology (CPT) codes for an injection that could include corticosteroids (64479, 64480, 64484, 84483, 77003, 76005, 62310, 62311, 20550, 20551, 20552, 20553, 20526, 20600, 20605, 20610, 62318, 62319) or CPT

codes for triamcinolone (acetamide or hexacetate). CPT codes for other exogenous steroid preparations were not searchable in RPDR. The study was approved by the Partners Human Research Committee.

We next validated the study population with a review of the electronic medical records (EMR) to confirm HIV infection. Documentation of any of the following in the EMR was considered confirmation of HIV infection: positive HIV Western blot or HIV RNA, inclusion of HIV in the patient's problem list, or prescription of antiretroviral medications other than for pre- or post-exposure prophylaxis.

We reviewed the charts of the patients with confirmed HIV-infection for details regarding the steroid injection by confirming the presence of a procedure note or other clinical documentation of a corticosteroid injection (e.g., epidural, intra-articular, nerve root block, trigger point, tendon sheath). For patients in whom multiple procedures were performed, we considered the last procedure in the study period to be the index procedure for each HIV-infected patient. Any additional steroid injections that were performed within the six months prior to the index injection were grouped together as the "injection series." Each subject was eligible for inclusion only once. Information was collected from the EMR regarding ART regimen at the time of each injection.

Those patients who underwent procedures without corticosteroid injection (e.g., anesthetic injection, aspiration) were excluded. Additionally, we excluded patients who had an injection but did not also receive their outpatient care at a Partners HealthCare institution (Infectious Diseases or primary care) as documented by outpatient notes in the EMR. We excluded patients who had a history of AI prior to injection or who had been prescribed oral corticosteroids within six months prior to corticosteroid injection as documented in the EMR (Figure 1a).

Case Definition – secondary adrenal insufficiency

We used a second query of RPDR to identify those patients within the cohort who were diagnosed with HPA-axis dysfunction after a steroid injection (Figure 1a). Patients with suspected HPA-axis dysfunction undergo a cosyntropin stimulation test (CST) or have measurement of a morning cortisol level. Because the physical exam features of HIV lipodystrophy can overlap with those of Cushing's syndrome, diagnostic testing with a CST or morning cortisol was used to confirm HPA-axis dysfunction and to distinguish it from lipodystrophy. As a result, we searched the study population by laboratory code for cortisol and ACTH to determine if there had been any assessment of the adrenal axis more than two weeks and less than six months following the index injection, given the most likely timing for exogenous steroid excess to disrupt the adrenal axis. Diagnosis of HPA-axis dysfunction was based on either a peak cortisol level <18 ug/dL within 30-60 minutes after stimulation with cosyntropin injection (250 mcg) or a morning cortisol <3 ug/dL. If available, an inappropriately low ACTH level was recorded (< 100 ug/dL), which distinguishes secondary AI from primary AI.

We systematically reviewed notes from all clinical encounters (with primary care physicians, infectious diseases specialists, endocrinologists, nurses, etc) to confirm clinical evidence of symptoms or signs consistent with HPA-axis dysfunction in this same time frame.¹² Search terms for symptoms or signs associated with steroid excess included fatigue, new opportunistic infection, mood changes, increased appetite or weight gain, new hypertension (i.e., $> 135/85$ mmHg in a patient not previously documented to have hypertension), abnormal fat deposition, proximal muscle weakness, skin changes such as atrophy, bruisability, striae, new cutaneous fungal infection. In addition to these symptoms or signs of steroid excess, we also searched for specific physical exam findings diagnostic of

Cushing's syndrome: new centripetal obesity, "moon face," hirsutism, or plethora.¹³ Search terms for symptoms or signs associated with AI included fatigue, weakness, myalgias, nausea, anorexia, orthostasis, and weight loss. Additional clinical data regarding the initial clinical presentation, as well as clinical follow-up regarding hospitalization(s), treatment(s) and time until resolution after diagnosis, were collected by use of a standardized chart abstraction tool.

Assessment of risk factors for HPA-axis dysfunction among HIV-infected patients on PI-based ART

During our preliminary analyses, we determined that all cases of HPA-axis dysfunction occurred among those patients who were treated with a PI at the time of a corticosteroid injection (Figure 1b); as a result, a more detailed data collection was performed among the subjects who were on PI treatment in order to characterize risk factors for HPA-axis dysfunction.

Data were collected by a detailed review of the EMR and included demographics (i.e., age, sex, race, weight), current immunologic and virologic status (i.e., T-cell subsets and HIV RNA within six months prior to or after the first steroid injection of the series), specific antiretroviral regimen, co-morbidities (i.e., diabetes, coronary artery disease, cirrhosis, chronic viral hepatitis, chronic kidney disease, malignancy) and social history (i.e., tobacco, alcohol, and injection drug use). A history of tuberculosis (latent or active) or disseminated cytomegalovirus was noted. Concurrent prescription of steroid medications other than oral was documented (e.g., topical, inhaled, intranasal), as well as co-prescription of other medications that are CYP3A4 inhibitors or inducers.

Additional details regarding the corticosteroid injections included the site(s) of injection, and the volume, potency and identity of the corticosteroid used in the injection series. The total number of steroid injections ever received by the patient was extracted from the EMR. Only details regarding the injections performed when the patient was prescribed PIs were collected in this second round of data extraction.

Chart review was conducted by two Infectious Disease physicians (EPH, BRW) and an Infectious Disease pharmacist (ESB). All staff members were trained rigorously in the specific chart abstraction tools and had extensive past experience in review of EMR at the institutions. Two reviewers independently completed all chart abstractions in order to verify the accuracy of the abstraction; discrepancies were resolved by direct review of the chart by both abstractors together. Study data were managed using Research Electronic Data Capture (REDCap) tools hosted at Partners, a secure, web-based application designed to support data capture for research studies.¹⁴ Data were double entered to ensure accuracy.

Statistical Analysis

For the data from HIV-infected patients on PI-based ART, univariate and multivariate Cox proportional hazards regression models were fitted to assess the impact of covariates of interest on time from index injection to diagnosis of HPA-axis dysfunction. Observations from patients who were not diagnosed with HPA-axis dysfunction were censored at 90 days after index injection; all cases of AI in our study group presented within this time frame, which is also supported by data from the general population.¹⁵

Covariates that were found to be statistically significant in univariate analyses were then advanced to the multivariate model. Sex and CD4 cell count (at the time of injection) were also included in the multivariate model given the potential for clinical relevance of these covariates.

Results

Using the initial RPDR search of the Partners database, we identified 457 patients with confirmed HIV-infection who received at least one injection during the study period (Figure 1a). Of these, 265 (58%) patients were excluded because review of the EMR did not confirm a corticosteroid injection on the date of billing (e.g., aspiration, injection with another substance, no procedure documented). Twelve patients were excluded because they did not receive primary care or HIV outpatient care at a Partners clinic and, therefore, follow-up of post-injection medical complications could not be assured. Ten patients were excluded because of history of AI prior to a corticosteroid injection or oral steroid use within six months before the index series (Figure 1a).

Of the 170 patients in the cohort, 81 (47.6%) patients were on ART that included a PI at the time of the steroid injection. Of the other 89 patients, 29 (17.1%) were not currently prescribed ART, 4 (2.4%) had an uncertain ART regimen, and 56 (32.9%) were taking ART that did not include a PI medication (Figure 1b).

Nine cases of HPA-axis dysfunction (event frequency, 5.3%; 95% CI, 2.4% - 9.8%) were diagnosed and confirmed based on abnormal cosyntropin stimulation tests, after presenting to clinical attention during the study period. We found no cases (0%; 95% CI, 0% - 4.1%) among patients who were not receiving PI-based ART. Of the 81 patients in the cohort who were on a PI-based regimen, nine (11.1%; 95% CI, 5.2% - 20.0%) presented to clinical attention with symptoms or signs of AI or steroid excess. Five patients had persistent clinical evidence of Cushing's syndrome at the time of diagnosis (Table 1).

Among those who developed HPA-axis dysfunction, three patients had received just one injection, two had received two injections, and four patients had been treated with three injections in the past six months (Table 2). Eight of the patients received injection(s) containing triamcinolone, and one patient received injections with methylprednisone. The median time to event among cases was 31 days after index injection (IQR 25-43 days), and no patient presented with clinical evidence of HPA-axis dysfunction more than 90 days after the index injection. Four patients (44.4%) required hospitalization during clinical workup for complications at the time of diagnosis. There were no deaths and no episodes of adrenal crisis. All nine patients were treated with 3-5 mg prednisone after diagnosis with HPA-axis dysfunction; duration of steroid replacement ranged from 1 week to more than three years. Three patients currently remain on steroid replacement despite being 2-3 years since initial diagnosis. All patients except for one were monitored by interval cosyntropin stimulation testing and were continued on steroid replacement until an appropriate stimulation response occurred; the sole patient whose recovery was not confirmed by cosyntropin stimulation had an uncomplicated steroid taper.

All cases of HPA-axis dysfunction occurred among patients on PIs, and the baseline demographics of these patients are shown in Table 2. The mean age was 51.5 years old, and 69% were male. The mean CD4 count was 569 cells/mm³ (range, 144-1354), and most patients (88.9%) were virologically suppressed on ART. Eight patients (9.9%) had diabetes mellitus, and five patients (6.2%) had known coronary artery disease. One patient had chronic obstructive pulmonary disease, and three patients had chronic kidney disease. Fifteen patients (18.5%) were known to be hepatitis C virus-infected, and four patients (4.9%) had chronic hepatitis B infection. No patients had a history of disseminated cytomegalovirus. Three patients (3.7%) had previously been treated for active tuberculosis, and four patients (4.9%) had completed treatment for latent tuberculosis. Twenty-five patients (30.9%) were current smokers, and 23 (28.4%) patients confirmed current or past alcohol abuse. No patients in the cohort admitted to actively using injection drugs, but 15

(18.5%) had a history of past abuse. Nineteen of the 81 patients (23.5%) had been prescribed an exogenous steroid preparation (e.g. topical, inhaled, intranasal, ophthalmic, or otic preparations) in the year prior to the index injection, and 10 (12.3%) were also prescribed another medication that interacts with CYP3A4. Only one of the patients subsequently diagnosed with HPA-axis dysfunction was concurrently prescribed an exogenous steroid preparation (e.g., inhaled, topical, etc); this patient, who was prescribed inhaled steroids, was diagnosed with HPA-axis dysfunction 36 days after an injection.

Data regarding the injection series were collected from the procedure notes. Triamcinolone (50.0%) (median dose 80 mg, range 10-80 mg) and methylprednisone (37.6%) (median dose 50 mg, range 40-120 mg) were the most frequently used steroid preparations; dexamethasone and betamethasone were used in a few patients. Most patients had been treated with fewer than five steroid injections between 2002-2011 and had received only one injection within the past six months (Table 2). Sites of injection were diverse with a great variety in the amount of steroid preparation used to inject similar sites.

Among those patients on PI-based ART, univariate analysis indicated that those at greater age and those treated with 2 injections or with greater amounts of steroid within six months were at higher risk of developing HPA-axis dysfunction (Table 3). Of note, we did not find a significant association between HPA-axis dysfunction and body mass index (BMI) or the prescription of other exogenous steroid preparations or other CYP3A4 inhibitors.

In multivariate analysis (Table 3), receipt of two or more steroid injections within six months remained significantly associated with subsequent development of clinically evident HPA-axis dysfunction (HR 6.42, [95% CI, 1.20-34.33, $p<0.05$]).

Discussion

In our retrospective cohort of HIV-infected patients who had local corticosteroid injections, nine cases of laboratory-confirmed HPA-axis dysfunction presented to clinical attention (overall event frequency, 5.2%); all cases occurred in patients who were treated with a PI (event frequency in this group, 11.1%). In patients on PI-based ART, the number of injections within the past six months was a risk factor for AI. Of those patients who developed HPA-axis dysfunction, no one presented symptomatically more than three months after the index injection.

The fact that all cases of HPA-axis dysfunction in this cohort occurred in patients who were treated with a PI underscores the significant concern regarding drug-interactions in this population. Considerable morbidity can result from either over- or under-dosing of essential medications. Corticosteroid levels are known to increase when administered with ritonavir and other PIs, which are CYP3A4 inhibitors and thus result in reduced clearance of steroid and prolonged supraphysiologic systemic levels.⁴ Interactions of PIs with inhaled steroid preparations have been well-described,³ but published data is less robust regarding complications related to steroid preparations administered by other routes (e.g., injections, otic, or topical preparations). Our data show that corticosteroid injections pose a substantial risk of disrupting the endogenous HPA-axis dysfunction in HIV-infected patients on PIs leading to clinical presentation with signs and symptoms of steroid excess or adrenal insufficiency.

In addition to short-term morbidity, the longer term outcomes of HPA-axis dysfunction in this population are not well-characterized. Given that HIV-infected patients are at increased risk for premature osteoporosis and cardiovascular disease,^{16, 17} it is possible that even limited durations of supraphysiologic steroid excess could have substantial adverse effects on a vulnerable population.¹⁸ Furthermore, although individuals may have clinical signs

consistent with steroid excess, they might not mount an adequate endogenous cortisol response in response to stressors such as acute illness so that periods of unrecognized AI may also result in additional morbidity. Because the need for local corticosteroid injections is likely to increase among an aging HIV population in the US during the coming years, such adverse events could become more frequent.

Although the number of steroid injections was significantly associated with clinically evident HPA-axis dysfunction in our cohort, the site of injection(s), the specific corticosteroid and specific protease inhibitors were not predictive of subsequent HPA-axis dysfunction. The amounts of steroid used in similar procedures were widely variable, which suggests that the indication for procedure and site of injection should not be considered in determination of risk to the patient. The total number of steroid injections over a relatively short period of time is a significant predictor of subsequent development of HPA-axis dysfunction. It might be possible to reduce the risk of this adverse event by decreasing the amount of corticosteroid used in these injections for this at risk population. Pharmacokinetics studies could also be helpful in future investigations.

At our institution, we have changed our clinical practice because of the high frequency of adverse events seen in this population. Improved multi-disciplinary communication between providers is crucial. We also have instituted a pharmacy alert for use of injectable steroid preparations; any practitioner who orders a corticosteroid for injection in an HIV-infected patient is reminded to discuss the procedure directly with an HIV provider. Additionally, we now counsel our HIV-infected patients who are treated with PIs against having corticosteroid injections if an alternative treatment is available. If no other treatment plan is feasible, then we consider a pre-emptive change to non-PI based ART if other antiretroviral options exist. HIV-infected patients who do not have an alternative ART regimen and require corticosteroid injection are followed closely in the 90 days following injection with careful attention to symptoms and signs of steroid excess or AI and a low threshold for diagnostic testing with either a morning cortisol or a cosyntropin stimulation test. At our institution, given the diurnal variation in cortisol values and logistical challenges, we have found the cosyntropin stimulation test to be a more reliable test as it is often difficult to obtain a true morning cortisol testing. For those patients who receive a corticosteroid injection and become symptomatic, we consider a switch to a PI-sparing regimen in order to minimize inhibition of CYP3A4 dependent metabolism of glucocorticoids. Because cobicistat also inhibits CYP3A4, we follow similar precautions in patients who receive this drug.

The major limitation of this study is its retrospective nature. We relied on previously collected clinical and medication information in the electronic record. Patient adherence to the medications listed in the record could not be confirmed. As a result, we were not able to assess co-prescription of opioids, the long-term use of which has also been associated with HPA-axis dysfunction; however, all cases in our cohort were temporally related to corticosteroid injection. The event frequency of 11.1% in patients on PI-containing ART is most likely an underestimate because diagnostic testing was pursued only if the clinician considered the diagnosis. Asymptomatic patients or those who did not present to clinical attention would not have been captured by our systematic search and are not represented in our analysis. Similarly, if a cortisol stimulation test is performed too soon after the initial exposure (< 6 weeks), the results could be falsely normal as it may take the adrenal cortex up to 6 weeks to atrophy and adjust to reduced ACTH secretion from the pituitary;¹³ in such cases, HPA-axis dysfunction would not have been identified given our search strategy. Estimation of a rate of HPA-axis dysfunction following injection was not possible because of the inherent difficulty of defining time at risk following injections of variable amounts at different sites and the retrospective nature of the study design. For these reasons, prospective

studies are needed to better characterize the incidence of adrenal axis dysfunction after corticosteroid injection. Finally, patients who either received a corticosteroid injection or were evaluated in follow-up at an institution outside of Partners HealthCare system would not have been captured by our search strategy or included in our cohort. The study population is from an academic tertiary care center in an urban setting and therefore may not be generalizable to other settings.

In conclusion, HPA-axis dysfunction is common among HIV-infected patients who are treated with a PI and have local corticosteroid injection(s). Corticosteroid injections in HIV-infected patients on PIs should only be used with great caution and close monitoring. For patients who require local corticosteroid injection, a preemptive change to a PI-sparing regimen should be considered; patients who cannot be safely changed to a PI-sparing regimen should be counseled regarding signs and symptoms of HPA-axis dysfunction prior to the procedure.

Acknowledgments

The authors thank Shawn Murphy and Henry Chueh and the Partners Health Care Research Patient Data Registry group for facilitating use of their database.

Funding: EPH is supported by National Institute of Allergy and Infectious Disease [T32 AI 007433]. RTG is supported by National Institutes of Health (NIH) [R01 AI066992-04A1] and NIH G08LM008830-01 and by grants to the AIDS Clinical Trials Group (NIH U01 AI 694722) and the Harvard University Center for AIDS Research (NIH 2P30 AI060354-06). This publication was made possible with help from the Harvard University Center for AIDS Research (CFAR), an NIH funded program (P30 AI060354), which is supported by the following NIH Co-Funding and Participating Institutes and Centers: NIAID, NCI, NICHD, NHLBI, NIDA, NIMH, NIA, FIC, and OAR

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Figure 1.

a. Protocol for selection of study population. Abbreviations: HIV, human immunodeficiency virus; **HPA**, **hypothalamic-pituitary-adrenal**; ID, Infectious Diseases; PCP, primary care physician; PI, protease inhibitor; ART, antiretroviral therapy.

b. Ascertainment of cases of **HPA-axis dysfunction** from the study population by search of the medical record for cosyntropin stimulation testing. All cases occurred among members

of the study population who were taking PI-based ART. Abbreviations: **HPA**, **hypothalamic-pituitary-adrenal**; HIV, human immunodeficiency virus; PI, protease inhibitor; ART, antiretroviral therapy.

Table 1

Characteristics of patients who were diagnosed with HPA-axis dysfunction after steroid injection.

Case	ART ^a	Adrenal insufficiency diagnosis (post-index injection day #)	Pre-stim Cortisol (ug/dL) ^b	Post-stim Cortisol (ug/dL) ^c	ACTH (ug/dL) ^d	Presenting symptoms	Signs on exam	Hospitalization for HPA-axis dysfunction
1	TDF FTC r/ATV	14	0.5	4.4		Fatigue Weakness Mood changes	None	No
2	TDF FTC r/ATV	43	1.8	9.5	9	Fatigue Weakness Anorexia	Thrush Skin atrophy Easy bruising	Yes
3	TDF FTC RAL r/DRV	30	<0.5	4.6	0	Fatigue Increased appetite	Weight gain Supraclavicular fat deposition New hypertension	No
4	ABC 3TC ENF FPV r/LPV	14	1.6	15.9	0	Fatigue Weakness Dizziness	Orthostasis New hypertension	Yes
5	3TC AZT ATV	31	<0.5	5.3	6	Fatigue Weakness Myalgias	Weight gain New facial swelling	No
6	TDF FTC ETR RAL r/DRV	54	1	9.8		Fatigue Weakness Myalgias Mood changes	Thrush Skin atrophy Easy bruising Cushingoid facial features	No
7	TDF FTC ATV	25	3.6	9.2	11	Excessive thirst Dysphagia	Weight loss Thrush	Yes
8	TDF FTC ATV	36	0.5	10.2	9	Weakness Nausea Dizziness	Skin atrophy Proximal myopathy	No
9	TDF FTC ATV	68	2.4	4.4	17	Fatigue Weakness	Cushingoid appearance New hypertension	Yes

Abbreviations: HPA, hypothalamic-pituitary-adrenal; ART, antiretroviral therapy; ACTH, adrenocorticotropic hormone; TDF, tenofovir; FTC, emtricitabine; r, ritonavir booster; ATV, atazanavir; RAL, raltegravir; DRV, darunavir; ABC, abacavir; 3TC, lamivudine; ENF, enfurvitide; FPV, fosamprenavir; LPV, lopinavir; AZT, zidovudine; ETR, etravirine.

^aProtease inhibitors are in bold.

^bCortisol level before cosyntropin injection given (baseline).

^cPeak cortisol level 30-60 minutes after cosyntropin injection (response to stimulation test).

^dNormal range 6-76 ug/dL; ACTH values <100 ug/dL are indicative of secondary adrenal insufficiency in setting of these cosyntropin stimulation tests.

Table 2
Baseline demographic data for 81 HIV-infected patients on PI-containing antiretroviral regimens who received concomitant local corticosteroid injection(s)

Covariate	Overall (n = 81)
Age (years) – mean (range)	51.5 (31.9 – 83.4)
Male gender – no. (%)	56 (69.1%)
Race – no. (%) ^a	
Caucasian	42 (54.5%)
Other	35 (45.5%)
Body mass index (kg/m ²) – mean (range)	28.2 (19.1– 42.5)
CD4 (cells/mm ³) at time of injection - no (%) ^{b,c}	
200	4 (5.1%)
200 - 500	31 (39.7%)
500	43 (55.1%)
Virologically suppressed (<200 copies/ml) – no. (%) ^c	72 (88.9%)
Prescription of exogenous non-systemic steroids within past year - no (%) ^d	19 (23.5%)
Total number of steroid injections - no (%) ^b	
1	39 (48.1%)
2-4	32 (39.5%)
5-9	7 (8.6%)
10	3 (3.7%)
Number of steroid injections in past 6 months – no (%)	
1	55 (67.9%)
2	16 (19.8%)
3	10 (12.3%)
Number of daily ritonavir doses – no (%)	
0	14 (17.3%)
1	35 (43.2%)
2	32 (39.5%)

Abbreviations: HIV, human immunodeficiency virus; PI, protease inhibitor; no, number.

^a 4 subjects without data in the medical record regarding race.

^b Percentages may not sum to 100% because of rounding.

^c Data available within 6 months of initial injection; 3 subjects without data in the medical record for CD4 count or HIV RNA.

^d Exogenous non-systemic steroid preparations include topical, inhaled, intranasal, ophthalmic, and otic preparations.

Table 3
Risk factors for HPA-axis dysfunction among HIV-infected patients on PI-based ART:
Univariate and multivariate Cox-regression analyses

Covariate	Univariate Cox Regression Hazard Ratio [95% CI]	p-value	Multivariate Cox Regression Hazard Ratio [95% CI]	p-value
Age (years)	1.05 [1.00 – 1.11]	0.07	1.03 [0.97 – 1.10]	0.33
Sex				
Female	1.00			
Male	1.65 [0.34 – 7.95]	0.53	1.86 [0.34 – 9.44]	0.49
Race				
Caucasian	1.00			
Other	0.32 [0.07 – 1.56]	0.16		
CD4 (cells/mm ³) at time of injection				
200	5.71 [0.52 – 63.01]	0.16	7.08 [0.61 – 81.68]	0.12
200 – 500	3.80 [0.74 – 19.58]	0.11	4.05 [0.75 – 21.93]	0.10
500	1.00		1.00	
Body mass index (kg/m ²)	1.03 [0.92 – 1.16]	0.58		
Prescription of exogenous non-systemic steroids within past year				
No	1.00			
Yes	1.09 [0.23 – 5.22]	0.92		
Total number of steroid injections				
<5	1.00			
≥ 5	2.02 [0.42, 9.73]	0.38		
Number of steroid injections in past 6 months – no (%)				
1	1.00		1.00	
≥2	4.71 [1.18 – 18.85]	0.03	6.42 [1.20 – 34.33]	0.03
Number of daily ritonavir doses				
0	1.00			
≥ 1	1.71 [0.21 – 13.67]	0.61		

Abbreviations: HPA, hypothalamic-pituitary-adrenal; HIV, human immunodeficiency virus; PI, protease inhibitor; ART, antiretroviral therapy; CI, confidence interval; no, number.