

## **Exogenous steroids, adrenal insufficiency and adrenal crisis—who is at risk and how should they be managed safely.**

**David Erskine- Specialist Pharmacy Services (SPS)  
Helen Simpson on behalf of Society for Endocrinology Steroid Emergency Card working group**

Endorsed by the Society for Endocrinology and the British Association of Dermatologists

### **Introduction**

Recently published guidance on the prevention and emergency management of adult patients with adrenal insufficiency (AI) (Simpson 2020) outlined the general issues relating to adrenal crisis. This was subsequently supported by an NHS England and NHS Improvement national patient safety alert (NatPSA) promoting the use of a new Steroid Emergency Card to support the early recognition and treatment of adrenal crisis in adults (NHSE/I 2020). This highlighted four deaths, four critical care admissions, and around 320 other incidents related to this issue in a two year period. Given variability of reporting, this is likely to be an underestimate of the incidents surrounding AI and adrenal crisis.

The NatPSA specified a number of actions that organisations need to implement to operationalise the introduction of the new Steroid Emergency Card. However it has become clear that many groups need support on how to identify patients at risk of AI from exogenous steroids, both for clinical safety around advice for patients undergoing surgery or invasive procedures, and to clarify who needs additional steroid cover for procedures, who needs to be given sick day rules advice and who requires a Steroid Emergency Card.

The purpose of this document is to offer guidance based on expert opinion (Society for Endocrinology (SfE) Steroid Emergency Card working group and Specialist Pharmacy Services) for challenging clinical issues around AI where there is no hard evidence in the medical literature;

The 4 areas of recommendation are:

1. Which patients are at risk of HPA axis suppression from exogenous steroids
2. Who should be issued with a Steroid Emergency Card and have sick day rules advice for intercurrent illness, procedures and surgery

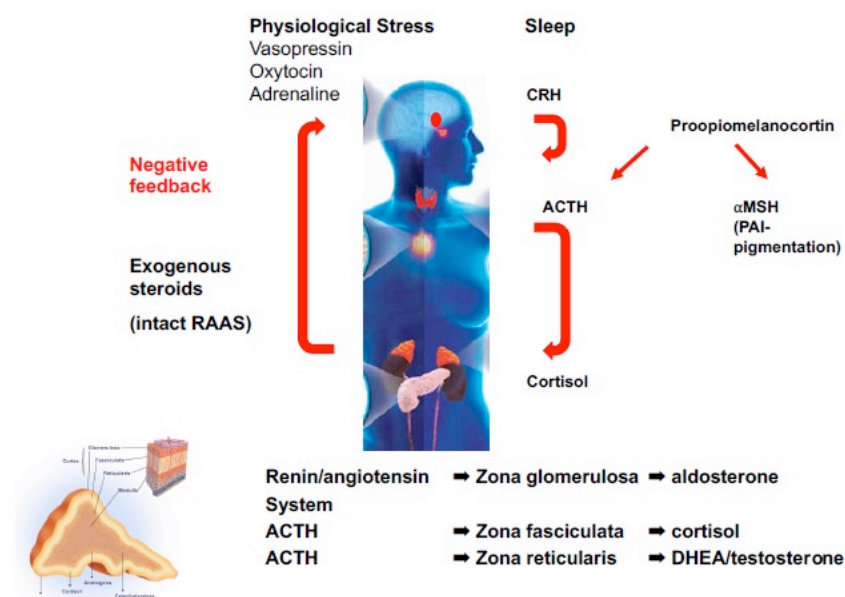
3. Who should have steroid cover for procedures, surgery and acute intercurrent illness
4. Who requires adrenal function assessment

## Background

Glucocorticoids (oral, intra-articular, intra-muscular, inhaled, nasal and topical preparations) are frequently used to treat a wide range of medical conditions. It is estimated that at any one time, approximately 1% of the UK population are on oral glucocorticoid therapy.

Prolonged use of glucocorticoids leads to negative feedback on the hypothalamic pituitary-adrenal (HPA) axis leading to a reduction in endogenous production of glucocorticoids. This results from reduced corticotrophin-releasing hormone (CRH) from the hypothalamus and adrenocorticotrophic hormone (ACTH) from the pituitary gland resulting in reduced or absent cortisol production by the adrenal glands (fig 1). Subsequent sudden cessation of exogenous glucocorticoids results in acquired secondary AI that may last for months to years after stopping glucocorticoids, and as stated by Broersen et al there is no administration form, treatment duration or underlying disease which can fully predict occurrence of HPA suppression (Broersen 2015).

Figure 1: Hypothalamo-pituitary-adrenal axis



The systemic use of glucocorticoids (mainly by oral administration) as anti-inflammatory and immunosuppressive therapy is the most common causes of AI. In

addition, dexamethasone, which is a highly potent synthetic glucocorticoid, is widely used as an antiemetic perioperatively and in oncology services. Currently dexamethasone is being used in the management of patients with COVID-19 requiring oxygen therapy -adrenal insufficiency should be considered for those on protracted or repeated courses of dexamethasone and/or other glucocorticoids (Matthay 2020). Whilst budesonide undergoes extensive inactivation during first-pass metabolism, it can be absorbed systemically and impact on adrenal function and patients higher dose or long term treatment are at risk of AI (Campieri 1997). HPA axis suppression may also occur through systemic absorption from inhaled steroid therapy, with about 10% of patients on high-dose steroid inhalers having evidence of HPA axis suppression (Woods 2015, Broersen 2015). Intra-articular glucocorticoids used for inflammatory and degenerative arthropathies can also be absorbed in the systemic circulation and are an established cause of AI (Broersen 2015).

HPA axis suppression may also occur through systemic absorption from inhaled steroid therapy, with about 10% of patients on high-dose steroid inhalers having evidence of HPA axis suppression (Woods 2015, Broerson 2015)

Surgery and sepsis are major physiological stressors, activating the HPA axis to produce glucocorticoid, predominantly cortisol. Patients with AI due to exogenous steroids are unable to mount an endogenous cortisol stress response, for example during surgery, invasive procedures, following trauma or when acutely unwell. Adrenal crisis can ensue and subsequent hypotension and shock can be fatal. All patients with AI of any cause, or who are considered at risk of AI, are at risk of adrenal crisis, and should be given stress doses of exogenous glucocorticoids at times which would normally provoke a cortisol stress response (ie during surgery or labour, for invasive procedures, following trauma or when acutely unwell) as per the Guidelines from the Association of Anaesthetists, the Royal College of Physicians and the Society for Endocrinology to maintain as near physiological concentrations of cortisol as possible (Woodcock 2020, Prete 2020)

Mehbratu et al (2019) reported a large cohort from primary care of 111,804 patients prescribed steroids. 184 described as having adrenal insufficiency, 248 Cushing's Syndrome from exogenous steroids, suggesting under-reporting. They also reported increase in hazards ratio (HR for adrenal dysfunction and death of 1.07 (95% CI: 1.04 to 1.09) for every increase of 5 mg per day and 2.25 (95% CI: 2.15 to 2.35) per 1000 mg of cumulative prednisolone-equivalent dose over the past year. HRs for Cushing's Syndrome were also increased with increased mortality.

## Drugs to note when considering adrenal function

### Drugs affecting glucocorticoid metabolism:

Certain drugs affect glucocorticoid metabolism which can result in AI. The commonest group are those affecting the activity of the drug-xenobiotic-metabolising enzyme CYP3A4. If a CYP3A4-inducer is given to a patient taking exogenous glucocorticoids

whose HPA axis is suppressed, the result can be adrenal crisis (as CYP3A4-inducers accelerate the clearance of glucocorticoids). If a CYP3A4-inhibitor is given to a patient taking exogenous glucocorticoid, the effects of the glucocorticoid can be potentiated leading to HPA axis suppression at unexpectedly low glucocorticoid doses. A full list of relevant drugs is listed in table 7.

#### **Drugs interfering with measurement of cortisol:**

Oral oestrogens (for example in the combined oral contraceptive pill or in HRT) increase cortisol binding globulin concentrations resulting in a higher plasma cortisol concentration. It is therefore difficult to assess adrenal function in people taking these drugs. Ideally, these should be stopped 6 weeks before attempts to assess the adrenal axis. If stopping the combined oral contraceptive pill, women should be advised to use other methods of contraception.

#### **Drugs interfering with adrenal steroidogenesis:**

Adrenal enzyme inhibitors (eg mitotane, etomidate, abiraterone, aminglutethimide, ketoconazole) all increase the risk of AI.

#### **Drugs affecting hypothalamo-pituitary function:**

Opiates, marijuana and checkpoint inhibitors used in oncology can all impair the HPA axis, potentially resulting in AI.

### **1. Which patients are at risk of HPA axis suppression?**

#### **Exogenous steroid preparations:**

##### **Long-term oral glucocorticoids**

Patients taking 5mg prednisolone or equivalent for longer than 4 weeks are at risk of HPA axis suppression (Sagar 2020) and adrenal crisis if physiologically stressed for instance during acute illness, surgery or other invasive procedures.

Prednisolone is used in the management of many inflammatory disorders for example polymyalgia rheumatica and giant cell arteritis.

Patients receiving long-term treatment with a glucocorticoid at the dosage presented in Table 1 should receive a Steroid Emergency Card

**Table 1: Long-term oral glucocorticoids (ie 4 weeks or longer)**

<b>Medicine</b>	<b>Dose (*)</b>
Beclometasone	625 microgram per day or more
Betamethasone	750 microgram per day or more
Budesonide	1.5mg per day or more (***)
Deflazacort	6mg per day or more
Dexamethasone	500 microgram per day or more (**)
Hydrocortisone	15mg per day or more (**)
Methylprednisolone	4mg per day or more
Prednisone	5mg per day or more
Prednisolone	5mg per day or more

(\*) dose equivalent from BNF except (\*\*) where dose reflects that described in the guideline by Simpson et al (2020) and (\*\*\*) based on best estimate.

### **Multiple doses of short-term glucocorticoids**

This is an area where there is little published evidence, however there is experiential and anecdotal evidence which supports the assertion that patients receiving multiple courses of prednisolone are at risk of HPA axis suppression and adrenal crisis when physiologically stressed (Fleishaker 2016) BTS guidelines have changed and patients with asthma and COPD are frequently given 5 to 7 day 'rescue' packs of steroids, often in combination with antibiotics, to self-administer during exacerbations. Ascertaining the number of rescue packs used in the past 12 months to attempt to assess the risk of AI can be difficult.

Oral dexamethasone is widely used in oncology as an antiemetic for patients receiving chemotherapy (e.g. 6mg daily for 4 days every 3 weeks to coincide with cycles of chemotherapy). Due to its antiemetic properties, dexamethasone is also frequently used peri-operatively. It can be difficult to identify when this has occurred as it may only be documented on an anaesthetic chart, and so may not be clearly seen on ward drug charts or within electronic records.

Patients may discharged from hospital having received prolonged courses of dexamethasone, some at high doses if part of an ARDS-type regimen, for severe Covid-19 infection and may be difficult to identify as that information may not have been communicated on discharge.

Patients described above and those receiving long-term treatment with a glucocorticoid at the dosage presented in Table 2 should receive a Steroid Emergency Card.

**Table 2: Short-term oral glucocorticoids (one week course or longer and has been on long-term course within the last year or has regular need for repeated courses)**

<b>Medicine</b>	<b>Dose (*)</b>
Beclometasone	5mg
Betamethasone	6mg per day or more
Budesonide	12mg (***)
Deflazacort	48mg per day or more
Dexamethasone	4mg per day or more (**)
Hydrocortisone	120mg per day or more (**)
Methylprednisolone	32mg per day or more
Prednisone	40mg per day or more
Prednisolone	40mg per day or more

(\*) dose equivalent from BNF except (\*\*) where dose reflects that given associated Guidance (Simpson et al 2020) and (\*\*\*) based on best estimate

### **Intra-articular glucocorticoid injections**

There are data demonstrating HPA axis suppression after a single intra-articular glucocorticoid injection. This can last up to 14 to 28 days (Habib, et al Clin Rheum 2014) and is, in part, dependent upon the dose and formulation of the intra-articular glucocorticoid used. In total, 52.2% of patients having intra-articular glucocorticoids have HPA suppression, however exact timing of this after intra-articular injection is unclear. In another review, it is reported that there is evidence to suggest that the amount of absorption from a single injection at standard doses is enough to cause short-lived but complete HPA axis suppression in most patients (Stout 2019). Similarly, in this review it is reported that 20% of patients given epidural glucocorticoids still had significant reductions in cortisol levels after 3 weeks.

A single intra-articular glucocorticoid injection is unlikely to permanently suppress the HPA axis, but if a patient has major surgery, trauma or intercurrent illness within 28 days of having an intra-articular glucocorticoids steroid injection, then they may be at risk of AI.

If a patient is receiving repeated intra-articular glucocorticoid injections, they should be considered at risk of HPA axis suppression. If they are also on an additional steroid, for example a moderately high-dose of inhaled glucocorticoid (see Table 4), then permanent HPA axis suppression can occur and further assessment should be considered.

## Inhaled glucocorticoids

High-dose inhaled steroids have been described as causing HPA axis suppression in about 10% of patients (Woods 2015, Broerson 2015). Budesonide and ciclesonide are approximately equipotent with beclomethasone (BDP), while fluticasone propionate (FP), mometasone and ultrafine particle BDP-HFA inhalers (Qvar® and Fostair®) are twice as potent as standard BDP inhalers (Paton 2006). Woods et al has shown that partial suppression of the adrenal response to ACTH is common (Woods EJE). It is possible that inhaled steroids can potentiate HPA suppression from steroids across other routes. Recommendations are to give a Steroid Emergency Card to patients receiving a total daily dose of >1000mcg for beclomethasone and >500mcg for fluticasone or equivalent.

Patients using an inhaled glucocorticoid at the doses described in Table 3 should be given a Steroid Emergency Card.

**Table 3: Inhaled glucocorticoid doses**

Medicine	Dose (*)
Beclomethasone (as non-proprietary, Clenil, Easihaler, or Soprobeq)	More than 1000 microgram per day
Beclomethasone (as Qvar, Kelhale or Fostair )	More than 500 microgram per day (check if using combination inhaler and MART regimen)
Budesonide	More than 500 microgram per day (check if using combination inhaler and MART regimen)
Ciclesonide	More than 480 microgram per day (**)
Fluticasone	More than 500 microgram per day
Mometasone	More than 800 microgram per day (**)

(\*) dose equivalent from BNF (1) except (\*\*) where dose reflects that given by London Respiratory Network (3)

## Nasal glucocorticoids

The guidance suggests an indicative threshold of 1000 micrograms per day. This limit is extremely unlikely to be reached using any of the “over the counter” preparations or available glucocorticoid sprays or drops for allergic rhinitis but may be an issue with

prescription drops used to treat nasal polyps. HPA axis suppression has been seen in a patient using both steroid nasal spray and steroid eye drops, however they were also on antiretroviral medications which may have potentiated the systemic effect of these on the HPA axis thus putting the patient at increased risk of AI during acute illness (table 7).

### **Nasal glucocorticoids plus inhaled glucocorticoids**

The London Respiratory Network suggest that the following dosage thresholds for inhaled glucocorticoid administered with a nasal glucocorticoid which may put the patient at increased risk of systemic effects.

Patients using nasal glucocorticoids and an inhaled glucocorticoid at the doses described in Table 4 should be given a Steroid Emergency Card.

**Table 4:**

Medicine	Dose
Beclometasone (as non-proprietary, Clenil, Easihaler, or Soprobeq)	800-1000 microgram per day
Beclometasone (as Qvar, Kelhale or Fostair )	400-500 microgram per day (check if using combination inhaler and MART regimen)
Budesonide	400-500 microgram per day (check if using combination inhaler and MART regimen)
Ciclesonide	320-480 microgram per day
Fluticasone	400-500 microgram per day
Mometasone	400-800 microgram per day or more

### **Steroid eye drops**

The guidance suggests an indicative threshold of 1000 micrograms per day. This limit is extremely unlikely to be reached using any of the available glucocorticoid eye drops for allergic conjunctivitis. If the patient is only on steroid eye drops, HPA axis suppression is unlikely. If a patient is taking other steroids by other routes then total exposure needs to be considered.



## Topical glucocorticoid creams and ointments

Whilst low dose topical steroids rarely cause adrenal insufficiency, potent and very potent glucocorticoids, can cause HPA axis suppression. Woods et al reported a rate of 15% but it should be noted this was in a small number of patients, and strength of topical glucocorticoid was not reported. One review has suggested that HPA axis suppression is limited to continuous use of very potent glucocorticoid over more than 28 days (Levin 2014). It is difficult to quantify the amount of systemic absorption, there have been estimates of 0.25% to 3% (Oakley 2016) and 0.5% to 30% (Walden 2011) of the dose applied to different parts of the body depending on thickness of skin, and vascularity. Suggested rates of absorption are:

- soles of the feet - 0.5%
- palms of the hands - 0.1%
- forearms - 1%
- armpits - 4%
- face - 7%
- eyelids and genitals - 30%.

Other factors that predispose to HPA axis suppression include chronic use, application to highly permeable areas such as the rectal or vaginal mucosa, treatment of large areas, use of occlusion, altered skin barrier (which is common in the conditions for which these medications are prescribed), and young age. HPA axis suppression and adrenal crisis has also been reported from use of skin-lightening creams containing steroid over large body surface areas (Khairy 2020).

The British Association of Dermatologists suggest that adults using a large quantity of potent or very potent glucocorticoids on extensive areas (e.g.  $\geq 200$  g of Clobetasol propionate 0.05% as Dermovate, ClobaDerm or equivalent per week) for 4 weeks or more may potentially be at increased risk of HPA suppression (see Table 5). They also suggest that any patient taking an inhaled corticosteroid at the doses outlined in Table 4 and a potent or very potent topical corticosteroid treatment for 4 weeks or longer should be considered at risk of HPA suppression. Similarly any patient requiring treatment with a potent or very potent corticosteroid and requiring regular courses of oral corticosteroids should also be considered to be at risk of HPA suppression.

Other patients may be at risk depending on the factors outlined above and these need to be assessed on a case-by-case basis.

Patients being treated with large quantities of potent or very potent topical glucocorticoids ( $\geq 200$ g per week) and those treated with potent or very potent topical glucocorticoids and significant amounts of other forms of glucocorticoid should be issued with a Steroid Emergency card.

**Table 5: Topical glucocorticoids.**

Topical steroid treatments	Potency of steroid
Beclometasone dipropionate 0.025%	Potent
Betamethasone dipropionate 0.05% and higher [incl Dalonev, Diprosone, Dovobet, Enstilar, in combination with clotrimazole (incl Lotriderm) and salicylic acid (incl Diprosalic)]	Potent
Betamethasone valerate 0.1% and higher [incl Audovate, Betacap, Betesil, Betnovate, Bettamousse, and in combination with clioquinol, fusidic acid (incl Fucibet, Xemacort) or neomycin]	Potent
Clobetasol propionate 0.05% and higher [incl. Clarelux, ClobaDerm, Dermovate, Etrivex and in combination with neomycin and nystatin]	Very potent
Diflucortolone valerate 0.1% [incl Nerisone]	Potent
Diflucortolone valerate 0.3% [incl Nerisone Forte]	Very Potent
Fluocinonide 0.05% [incl Metosyn]	Potent
Fluocinolone acetonide 0.025% [(incl. Synalar) and in combination with clioquinol (incl Synalar C)]	Potent
Fluticasone propionate 0.05% [incl Cutivate]	Potent
Hydrocortisone butyrate 0.1% [incl Locoid]	Potent
Mometasone 0.1% [incl Elocon]	Potent
Triamcinolone acetonide 0.1% [incl Aureocort]	Potent

All other topical glucocorticoids available in the UK are either mild or moderate potency

### **Rectal glucocorticoids**

There are some reports of rectal glucocorticoids causing adrenal insufficiency when used for inflammatory bowel disease (Luman 1994; Marshall 1997). Table 6 gives an outline of clinically significant glucocorticoid doses in rectal formulations. Using other rectal formulations would be unlikely to lead to HPA suppression. HPA axis suppression has been reported when topical steroids are used on the rectal mucosa

for pruritus ani (see section on topical steroids). Again, co-administration of steroids via other routes must be considered when assessing individual risk.

**Table 6: Rectal treatments which contain significant amounts of glucocorticoid**

Formulation	Dose
Budesonide enema	contains 2mg per dose
Budesonide rectal foam	contains 2mg per dose
Prednisolone rectal solution	contains 20mg per dose
Prednisolone suppositories	Contains 5mg per dose

## 2. Who should be issued with a Steroid Emergency Card?

Below are the groups of patients, receiving exogenous glucocorticoids and therefore at risk of AI, who need a Steroid Emergency Card. They should be given cover with hydrocortisone if admitted to hospital unwell (Simpson et al) or when undergoing a surgical or invasive procedure (Woodcock et al)

- Patients who have received a long-term course of glucocorticoids at a dose equivalent or higher than prednisolone 5mg (see Table 1)
- 3 or more short courses of high-dose oral glucocorticoids within the last 12 months, and for 12 months after stopping (see Table 2)
- 3 or more intra-articular/intramuscular glucocorticoid injections within the last 12 months, and for 12 months after stopping
- Repeated courses of dexamethasone as an antiemetic in oncology regimens, and for 12 months after stopping (the Steroid Emergency Card should be given on first cycle of dexamethasone) when future cycles are anticipated.
- Prolonged courses of dexamethasone (>10 days) for the treatment of severe Covid-19
- Inhaled steroids >1000mcg/day beclomethasone or >500mcg/day fluticasone (or equivalent dose of another glucocorticoid), and for 12 months after stopping (see Table 3)

- Patients taking inhaled corticosteroids at doses described in Table 4 and any other form of glucocorticoid treatment (incl potent/very potent topical glucocorticoids, intra-articular injection, regular nasal glucocorticoids).
- Topical high-dose ( $\geq 200\text{g/week}$ ) potent or very potent glucocorticoids used across a large area of skin for 4 weeks or more, or factors increasing absorption assessed on a case by case basis, and for 12 months after stopping. (see Table 5)
- Potent or very potent topical glucocorticoids applied to the rectal or genital areas and used at high dose (more than 30g per month) for more than 4 weeks, and for 12 months after stopping
- Patients prescribed any form of ongoing glucocorticoid treatment (except small amounts of a mild or moderate topical glucocorticoid which should be assessed on a case by case basis) in conjunction with medicines known to be potent CYP3A4 inhibitors (see Table 7)

### 3. Who should be given a Steroid Emergency Card and “sick day rules” advice

These are the patients on exogenous steroids at increased risk of AI needing a Steroid Emergency Card and advice regarding “sick day rules” if unwell outside of hospital. These groups are at greater risk of significant HPA axis suppression. They require cover with hydrocortisone if admitted to hospital unwell (Simpson et al) or when undergoing a surgical or invasive procedure (Woodcock et al).

- Patients taking oral prednisolone 5mg or above (or equivalent dose of other oral glucocorticoids) for more than 4 weeks, and for 12 months after stopping oral steroids (see Table 1)
- Patients receiving intra-articular or intramuscular glucocorticoid injections who also use glucocorticoids by another route (eg inhaled steroids, oral steroids etc)
- Concomitant use of CYP3A4 enzyme inhibitors (see list below) and glucocorticoids (any route of administration except small amounts of topical mild or moderate potency glucocorticoid which should be assessed on a case by case basis)
- Patients with respiratory disease such as COPD and asthma on high dose inhaled steroids receiving repeated courses of oral steroids (3 or more courses over the past 6 months).

### 4. Who should have steroid cover for intercurrent illness, invasive procedures and surgery?

Any patients carrying a Steroid Emergency Card, that is all patients listed above, should have steroid cover when acutely unwell or if having surgery or undergoing an invasive procedure such as endoscopy (Woodcock et al).

#### Notes:

- a. There is no need for these patients to be issued with an emergency hydrocortisone injection kit unless there is specific clinical concern.
- b. There is increased risk of AI when steroids are used across multiple routes eg. intra-articular, oral, inhaled, topical). If there is doubt or clinical concern then a Steroid Emergency Card should be issued.
- c. In the presence of hypotension, tachycardia, vomiting, hyponatraemia after surgery or an invasive post-procedure, or protracted course of glucocorticoid such as for Covid-19 there should be a low threshold for steroid cover.
- d. For more endocrinology resources and information on sick day rules please go to <https://www.endocrinology.org/adrenal-crisis>

### **Table 7. CYP3A4 enzyme inhibitors increasing cortisol concentration and risk of HPA axis suppression**

Patients prescribed any form of ongoing glucocorticoid treatment, at any dose, in conjunction with any of the medications below which are potent CYP3A4 inhibitors, should be issued with a Steroid Emergency Card

#### **Potent Protease inhibitors:**

Atazanavir  
Darunavir  
Fosamprenavir  
Ritonavir (+/- lopinavir)  
Saquinavir  
Tipranavir

#### **Antifungals:**

Itraconazole  
Ketoconazole  
Voriconazole  
Posaconazole

#### **Antibiotics:**

Clarithromycin—long term courses only

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