Dexamethasone is a dose-dependent perpetrator of drug–drug interactions: implications for use in people living with HIV

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Introduction

Dexamethasone is both a substrate and a dose-dependent inducer of cytochrome P450 3A4 (CYP3A4). Since many antiretroviral agents (ARVs) are substrates and/or inhibitors or inducers of CYP3A4, there is concern about drug–drug interactions (DDIs) with dexamethasone. However, the dose-dependent inducing effect of dexamethasone makes the interpretation of DDIs with ARVs complex given the broad range of dexamethasone doses and treatment durations in clinical use.

The question related to the DDI potential of dexamethasone has re-emerged with the prominent role of dexamethasone in the treatment of COVID-19 patients. Studies suggest that people living with HIV (PLWH) are at increased risk for severe clinical COVID-19 outcomes, in particular those having low CD4 cell counts or untreated HIV infection. Dexamethasone at a low dose of 6 mg/day for a maximum of 10 days has been shown to have a beneficial effect in hospitalized COVID-19 patients with a severe disease and requiring oxygen support (RECOVERY trial). Higher doses of dexamethasone (up to 20 mg/day) are currently being investigated in other COVID-19 trials. Besides COVID-19, dexamethasone is used for multiple conditions at daily doses ranging generally from 0.5 up to 40 mg and with variable treatment durations (i.e. single dose, short, intermittent, or chronic treatments).

Another difficulty relates to the fact that DDIs with dexamethasone have been evaluated only for a limited number of drugs, which do not include ARVs. This short review summarizes available in vitro and in vivo data on the DDI potential of dexamethasone and extrapolates these to recommendations for the management of DDIs with ARVs, considering various dexamethasone dosages and treatment durations.

Dexamethasone as perpetrator of DDIs

In vitro studies in primary cultures of human hepatocytes have shown that dexamethasone is a concentration-dependent CYP3A4 inducer. Dexamethasone-mediated CYP3A4 induction occurs through direct activation of pregnane X receptor (PXR), and by activation of glucocorticoid receptors which induce expression of PXR and constitutive androstane receptor, resulting in increased transcription of CYP3A4 enzymes. McCune et al. studied the in vitro effect of increasing dexamethasone concentrations on its ability to induce CYP3A4 in human hepatocytes. Activity of CYP3A4 increased by 1.7-, 1.9-, 3.9-, 6.9- and 6.6-fold on average after exposure to dexamethasone at 2, 10, 50, 100, or 250 µM concentrations, respectively. These concentrations will likely not be achieved in vivo; average steady-state dexamethasone plasma concentrations at 0.5–3 h after administration of 8 mg dexamethasone twice daily (q12h) were 0.10 µM (±0.078) in healthy adults. Martin et al. found the expression of CYP3A4 mRNA to be increased in human hepatic (HepG2) and intestinal cells (Caco-2) after incubation with dexamethasone concentrations ranging from 0.01 to 100 µM. Significantly higher expression of CYP3A4 mRNA was seen after incubation with 0.01 µM dexamethasone that further increased with higher dexamethasone concentrations (+45%–90% in HepG2; +10%–35% in Caco-2).

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in vitro studies support concentration-dependent induction of CYP3A4 by dexamethasone. Extrapolation from in vitro to in vivo data is challenging as laboratory data do not account for protein binding and hepatic drug uptake.

A few clinical pharmacokinetic studies have determined the effect of concomitant dexamethasone on CYP3A4 substrates. Villikka et al.8 investigated the impact of dexamethasone (1.5 mg q24h for 4 days) on the pharmacokinetics of 0.5 mg of triazolam, which is a CYP3A4 substrate. Triazolam exposure (i.e. AUC) decreased by 19% (not statistically significant) when it was taken together with dexamethasone.9 Both McCune et al.6 and Watkins et al.9 applied the erythromycin breath test to assess the effect of dexamethasone on hepatic CYP3A4 activity. The latter found a 55% increase of hepatic CYP3A4 activity in five patients after the administration of 16–24 mg/day dexamethasone dosed for 2–9 days.9 The other study reported a 26% increase of hepatic CYP3A4 activity after dexamethasone 8 mg was taken q12h for 5 days.6 Steady-state trough concentrations of crizotinib (mainly metabolized by CYP3A4) were comparable during long-term concurrent dexamethasone treatment (>21 days treatment; dose unknown) compared with crizotinib exposure observed 14 days after discontinuation of dexamethasone.10 However, trough concentrations of its main metabolite (completely metabolized by CYP3A4) were about 29% lower during dexamethasone treatment.10 Another clinical study evaluating cyclophosphamide pharmacokinetics following a single dose of dexamethasone 10 mg given IV reported a 2-fold increase in cyclophosphamide clearance in adults.11 The authors were unable to conclude whether the increased clearance was due to dexamethasone or cyclophosphamide auto-induction. In children receiving 8–16 mg/day dexamethasone for at least 5 days, cyclophosphamide clearance was increased by 80% compared with children not receiving dexamethasone.12 Teo et al.13 looked at hepatotoxicity during treatment with lapatinib in a nested case-control study based on data from 120 patients. Lapatinib is predominantly metabolized by CYP3A4 into a potentially hepatotoxic metabolite. Patients receiving lapatinib together with a median dose of 8 mg/day (range 1–16 mg) dexamethasone had a 4.6-times higher likelihood of developing hepatotoxicity, possibly due to induction of CYP3A4 and formation of reactive metabolites.13 These limited clinical data are consistent with in vitro observations showing that dexamethasone causes a dose-dependent induction of CYP3A4. Apart from CYP3A4, dexamethasone has also demonstrated in vitro inducing effects on CYP1A, CYP2C, UGT1A1, as well as the transporter P-glycoprotein.14–16 However, this has not been studied in vivo.

Dexamethasone was shown to be a more potent inducer of CYP3A4 compared with other corticosteroids based on PXR activation studies.14 However, clinical DDI studies with various CYP3A4 substrates have shown inconsistent findings. Villikka et al.17 found no significant impact of methylprednisolone on the pharmacokinetics of triazolam in 10 healthy subjects receiving a single dose of 32 mg methylprednisolone or 8 mg q24h for 9 days. Marcantonio et al.18 reported no significant effect of prednisone (10 mg q24h for 28 days) on midazolam and odanacatib.18 In contrast, another study reported a dose-dependent increase (11%–36%) in tacrolimus trough levels after withdrawal of prednisone (5 or 10 mg daily for 3 months) in 84 renal allograft recipients.19

Dexamethasone as a victim of DDIs

Dexamethasone is primarily metabolized by CYP3A4 and can therefore also be a victim of DDIs in the presence of inducers or inhibitors of this enzyme. Co-administration of a single dose of dexamethasone 5.0 mg IV or 4.5 mg oral and 200 mg of itraconazole (a strong CYP3A4 inhibitor) increased dexamethasone exposure by 3–4-fold in a cross-over study that included eight healthy subjects.20 Careful monitoring of dexamethasone toxicity when being co-administered with CYP3A4 inhibitors was recommended by the authors. On the other hand, the mean oral bioavailability of dexamethasone was reduced by 60% in six patients receiving a dose of 4 mg dexamethasone orally with phenytoin (a strong CYP3A4 inducer) compared with nine patients receiving dexamethasone alone in an open-label study.21 The authors suggested a 4-fold dose increase of dexamethasone in the presence of phenytoin to overcome the interaction.21

Recommendations for the management of DDIs with ARVs

Dexamethasone dosage and treatment duration vary based on the medical conditions being treated. Due to the dose-dependent inducing effect of dexamethasone, there will be differences in the DDI risk depending on the dosage regimen. Figure 1 provides a proposed categorization of dexamethasone inducing effect for selected medical conditions based on recommended dosage and treatment duration.22 The categories are based on the FDA classification for inducers: weak and moderate inducers decrease the AUC of CYP3A4 substrates by >20% to <50% and >50% to <80%, respectively.23 A dexamethasone dose of 1.5 mg/day is unlikely to cause a significant inducing effect as shown by Villikka et al.8 Based on findings from by McCune et al.,6 daily dosages up to 16 mg given for a short period of time are expected to cause a weak inducing effect. Multiple daily doses >16 mg dexamethasone were found to cause moderate induction as detailed by Watkins et al.9 To our knowledge, the effect of intermittent use of corticosteroids on induction of CYP3A4 has not been studied. The weekly administration of another CYP3A4 inducer, rifapentine used for the treatment of latent TB infection, has shown that induction is time dependent with the strongest induction observed between 2 and 6 days after drug administration.24–26 Even though the overall induction was found to be less pronounced during weekly use (900 mg for 3 weeks) compared with q12h use of rifapentine (400 mg for 4 days), it is clinically relevant.27 Hence, the same dosing recommendations could be adopted for intermittent use of dexamethasone given that the dosing interval is ≤7 days. In rare cases where dexamethasone is prescribed as a regimen with dosing intervals longer than 7 days, these can be considered as being single doses of dexamethasone.

Rifabutin used for the treatment of TB is a moderate inducer of CYP3A4. DDIs between rifabutin and ARVs have been studied extensively in patients and healthy volunteers, since concomitant use during HIV/TB co-infection is common.27,28 Therefore, the management of DDIs between rifabutin and ARVs is a useful marker for extrapolation as a high daily dose of dexamethasone is also expected to cause a moderate inducing effect.27 Similar to rifabutin, dose adjustments should be maintained for at least 2 weeks after cessation of dexamethasone treatment due to the persistent
inducing effect following discontinuation of an inducer and considering also the long elimination half-life of these drugs.

Doravirine, rilpivirine and maraviroc are mainly metabolized by CYP3A4. Co-administration of doravirine or rilpivirine with 300 mg rifabutin resulted in an ~50% decrease in exposure for both compounds. Rifabutin was shown to decrease maraviroc exposure and trough concentration by 17% and 30%, respectively, and maraviroc exposure decreased by ~50% when co-administered with efavirenz. To overcome these interactions, the product labels recommend to increase doravirine dosage from 100 mg once daily (q24h) to 100 mg q12h; to double rilpivirine dosage to 50 mg q24h; and to increase maraviroc dosage to 600 mg q12h if given with a moderate inducer (but without a PI or any other strong CYP3A4 inhibitor). Doubling the dose of doravirine and maraviroc can be applied even in the case of a weak inducing effect of dexamethasone, because there are minimal safety concerns. However, feasibility of dose adjustments for these ARVs in the case of weak induction by dexamethasone should be weighed per patient and take into consideration availability of therapeutic drug monitoring (TDM) and increased dosing frequency, pill burden and costs. The rilpivirine product label recommends against its use together with systemic dexamethasone (except as a single dose) as a significant decrease in rilpivirine exposure may occur. Therefore, high-dose dexamethasone and long-term treatment courses are contra-indicated with rilpivirine. No comments are made about doubling the rilpivirine dose, although whether this is due to concerns about the risk of QT interval prolongation is not clear. It should be noted that rilpivirine was associated with an increased risk of QT interval prolongation at a supra-therapeutic daily dose of 75 mg, which resulted in a mean 2.6-fold increase in $C_{\text{max}}$ compared with the standard dosage. However, the co-administration of rilpivirine 50 mg q24h with rifabutin resulted in an increase in rilpivirine $C_{\text{max}}$ of 43% compared with rilpivirine 25 mg alone, thus the risk of a QT interval prolongation when doubling rilpivirine dosage in the presence of an inducer can be considered to be low. Doubling the dose of rilpivirine to 50 mg q24h in the presence of low to moderate dosages of dexamethasone for a short treatment period (<10 days) is unlikely to result in HIV treatment failure or toxicity.

Nevirapine, etravirine and efavirenz are unlikely to be significantly affected by dexamethasone because they already induce their own metabolism (auto-induction). At the higher dose of dexamethasone, the induction effect of dexamethasone and the ARVs is likely to be comparable so that a decrease in dexamethasone exposure is less of a concern. No $a\, priori$ increase in dexamethasone is required but a dose increase considered if clinically needed. However, when using a low dose of dexamethasone (as in the RECOVERY trial), exposure of dexamethasone is expected to be reduced by these ARVs so that a dosage increase would be recommended. Temsavir, fostemsavir’s active metabolite, is mainly metabolized by esterase-mediated hydrolysis and to a lesser extent by CYP3A4. Co-administration of fostemsavir with rifabutin 300 mg q24h resulted in a reduction of 27%, 30% and 41% in $C_{\text{max}}$, AUC and $C_{\text{min}}$, respectively. This observed decrease is considered not to be clinically relevant; hence, no additional monitoring is needed for fostemsavir co-administered with both low and high doses of dexamethasone.

Given the strong inhibitory effect of boosted PIs on CYP3A4, the use of high-dose dexamethasone and long-term use pose an increased risk of developing a Cushing syndrome due to increased dexamethasone exposure. On the other hand, high dosages of dexamethasone could also result in a reduced exposure of the boosted PIs. Ritonavir-boosted PIs seem less affected by moderate CYP3A4 induction compared with cobicistat-boosted PIs or elvitegravir. Differences in pharmacokinetics relating to the two boosters are also seen in the presence of efavirenz or in pregnancy. Thus, co-administration of boosted PIs, in particular by cobicistat, with high-dose dexamethasone warrants caution with recommended monitoring of ARV efficacy and symptoms of hypercortisolism. The risk of developing a Cushing syndrome, due to inhibition

| Short treatment course | Low dose | Moderate dose | High dose |
|------------------------|----------|--------------|----------|
| 1<10 days              | Cushing syndrome diagnosis | COVID-19<sup>a</sup> | COVID-19<sup>b</sup> |
|                        |          | Antimicrobial | Bacterial meningitis |
|                        |          | Ashma | Immune thrombocytopenia |
| Long treatment course  | Adrenal hyperplasia | Palliative care | Multiple myeloma |
| >10 days               |          | Cerebral oedema | Tuberculosis meningitis |
|                        |          | Cerebral toxoplasmosis | |

Figure 1. Dexamethasone CYP3A4 inducing effect considering various dosing and treatment duration for selected conditions. White, very low risk for causing clinical significant interactions; light grey, low risk for causing clinical significant interactions; darker grey, moderate risk for causing clinical significant interactions. Intermittent use of dexamethasone with dosing intervals of <7 days follow the same dose recommendations as the daily doses referred to in this figure. For dosing intervals >7 days, these can be considered as being single gifts of dexamethasone. Categorization of induction potential according to FDA classification. The classification for dexamethasone is based on limited clinical data that are currently available for dexamethasone’s induction potential, reported in this review. RECOVERY trial: dexamethasone administered at 6 mg q24h for 10 days; SPIDEX-II trial: dexamethasone administered at 2 mg q12h for 12 days; NCT04452565 trial: dexamethasone administered at 8 mg q12h for 1 day, followed by 4 mg q24h for 5 days; NCT0463729 trial: dexamethasone administered at 8 mg q24h for 5 days; NCT04676979 trial: dexamethasone administered at 10 mg q24h for 5 days, followed by 5 mg q24h for up to 5 days, followed by 2.5 mg/day for up to 4 days; COVID STEROID 2 trial: dexamethasone administered at 12 mg q24h or 6 mg q24h for 10 days; NCT04395105 trial: dexamethasone administered at 16 mg q24h for 5 days, followed by 8 mg q24h for 5 days. CoDEX, DEXA-REFINE, REMED, DHYSO, HIGHLWDEXA trials: dexamethasone administered at 20 mg q24h for 5 days, followed by 10 mg q24h for 5 days; ROIDS-Dose trial: dexamethasone administered at 0.2 mg/kg/day dexamethasone (maximum 20 mg daily) for 10 days.
Figure 2. Recommendations for the management of DDIs between dexamethasone and ARVs based on dexamethasone dosage and duration of treatment. Dosage adjustments should be considered during the concurrent administration of dexamethasone and up to 2 weeks after the end of dexamethasone treatment due to the persisting inducer effect. Green, no clinically significant interaction; yellow, potential weak interaction not requiring a priori action; amber, potential clinically relevant interaction requiring monitoring or dose adjustment; red, contra-indicated. Recommendations do not apply to dexamethasone dosages of ≤1.5 mg/day as these low doses are not expected to cause clinically relevant DDIs. However, DDIs where ARVs affect dexamethasone exposures should be considered for these cases. Dexamethasone >1.5–16 mg daily dose and short treatment course (1–10 days). Dexamethasone >16 mg daily dose and short or long treatment course (≥10 days). DOR, doravirine; MVC, maraviroc; RPV, rilpivirine; EFV, efavirenz; ETV etravirine; NVP, nevirapine; FTR, fosamprenavir; ATV/r, atazanavir/ritonavir; DRV/r, darunavir/ritonavir; LPV/r, lopinavir/ritonavir; ATV/c, atazanavir/cobicistat; DRV/c, darunavir/cobicistat; EVG/c, elvitegravir/cobicistat; DTG, dolutegravir; RAL, raltegravir; BIC, bictegravir; RPV/CAB, rilpivirine/cabotegravir; LA, long-acting; ARV, antiretroviral agent; q24h, once daily; q12h, twice daily. This figure appears in colour in the online version of JAC and in black and white in the print version of JAC.

| Antiretroviral | Low risk of clinical significant interactions caused by dexamethasone | Moderate risk of clinical significant interactions caused by dexamethasone |
|---------------|---------------------------------------------------------------|---------------------------------------------------------------------|
| DOR           | Consider increase DOR dosage to 100 mg q12h.                | Increase DOR dosage to 100 mg q12h.                               |
| MVC           | Consider increase MVC dosage to 600 mg q12h in absence of PI or other strong CYP3A4 inhibitors; Reduce MVC dosage at 150 mg q12h in presence of PI or other strong inhibitors. | Increase MVC dosage to 600 mg q12h in absence of PI or other strong CYP3A4 inhibitors; Reduce MVC dosage at 150 mg q12h in presence of PI or other strong inhibitors. |
| RPV           | Consider increase RPV dosage to 50 mg q24h in case substitution to another corticosteroid is undesirable. | Contra-indicated in label. DDIs may be overcome with RPV 50 mg q24h based on rifabutin DDIs. |
| EFV ETV NVP   | Dexmethasone clearance is increased due to induction of CYP3A4 by EFV, ETV and NVP. Double dexamethasone dosage. No significant reduction of antiretroviral drug concentrations expected due to dexamethasone. | Dexmethasone clearance is increased due to induction of CYP3A4 by EFV, ETV and NVP. Consider increasing dexamethasone dose if clinically needed. No significant reduction of antiretroviral drug concentrations expected due to dexamethasone. |
| FTR           | Weak reduction in tenofovir (active metabolite of FTC) exposure not considered to be clinically relevant. No additional monitoring needed. | Tenofovir (active metabolite of FTC) exposure reduced by 30% with rifabutin (moderate inducer), comparable decrease expected with high-dose dexamethasone, but this is not considered to be clinically relevant. No additional monitoring needed. |
| ATV/r DRV/r LPV/r | No dosage adjustment needed. Minimal risk of Cushing syndrome. | Antiretroviral drug exposure may be reduced particularly with high dose and long-term use of dexamethasone. Use with caution, monitor antiviral response and perform TDM where available. |
| ATV/c DRV/c EVG/c | No dosage adjustment needed. Minimal risk of Cushing syndrome. | Co-administration is not recommended as it may significantly decrease cobicistat plasma concentrations (based on efavirenz DDIs) and consequently those of the boosted ARV. |
| DTG RAL       | No dosage adjustment needed. | No dosage adjustment needed. |
| BIC           | Weak reduction in bictegravir exposure expected, but not clinically relevant. No additional monitoring needed. | Bictegravir exposure reduced by 40% with rifabutin (moderate inducer), comparable decrease expected with high-dose dexamethasone. Use with caution, additional monitoring of antiviral response recommended and perform TDM where available. |
| RPV/CAB LA   | Contra-indicated in label. No recommendations on how to manage DDIs with LA ARVs. | Contra-indicated in label. No recommendations on how to manage DDIs with LA ARVs. |
of dexamethasone metabolism by PIs, is less likely to occur when using low-dose and short-term treatment courses of the corticosteroid. Also, low dose of dexamethasone is unlikely to significantly alter the exposure of PIs.

The unboosted integrase inhibitors raltegravir and dolutegravir are predominantly metabolized by UGT1A1 and therefore are not expected to be significantly affected by dexamethasone. However, it should be noted that potential UGT1A1 induction by dexamethasone has not been studied in humans. In vitro data are contradicting as transcription of UGT1A1 mRNA was found to be induced by 33%–78% in rat hepatocytes, while incubation of human hepatocytes with high concentrations of dexamethasone did not affect glucuronidation of estradiol. Bictegravir is metabolized 50% by CYP3A4. In the presence of rifampin, a 40% decrease in bictegravir exposure was shown, which deserves caution considering its efficacy margin of 0.5-fold. Therefore, monitoring of viral response or TDM of bictegravir (where available) are advised when using a long-term treatment course or high dose of dexamethasone. A low to moderate dose of dexamethasone is expected to cause a small decrease in bictegravir exposure, but no additional monitoring is needed a priori.

The novel long-acting (LA) ARVs cabotegravir and rilpivirine pose a new challenge, as there are currently no recommendations on how to overcome DDIs with the intramuscular administration of these drugs. Rilpivirine concentrations are expected to decrease in the presence of high-dose dexamethasone treatment and could also be affected by moderate doses of dexamethasone. Until we have further data on how to manage DDIs with LA ARVs, co-administration is contra-indicated. Further research is needed to determine whether supplementing additional oral rilpivirine in the presence of a moderate CYP3A4 inducer can overcome the DDI.

If available, TDM constitutes a useful approach to monitor and manage DDIs. Substitution of dexamethasone with another corticosteroid devoid of inducing properties, such as (methyl)prednisolone, can also be considered if the ARVs cannot be changed or dose adjusted.

All recommendations for management of DDIs between dexamethasone and ARVs are summarized in Figure 2. Various online resources are available to aid healthcare professionals to manage DDIs in PLWH and COVID-19 patients, e.g. www.hiv-druginteractions.org and www.covid19-druginteractions.org. Product labels provide lists of interacting medications based on findings from DDIs studies, as well as warnings for medications where a clinically relevant interaction is suspected. However, these lists are often incomplete, because post-marketing data from DDIs studies, case reports and TDM registries provide additional sources for guidance on the management of DDIs. As a result, for some ARVs, the product label does not mention dexamethasone in the list of interacting medications, while DDI resources do identify a potential interaction with dexamethasone. For some of the potential interactions between ARVs and dexamethasone, recommendations to overcome the interactions can differ slightly among various DDI resources. This often relates to differences in dexamethasone dose as most resources do not distinguish between low and high doses of dexamethasone, whereas others, such as the COVID-19 interaction database, provide recommendations for a specific dose of dexamethasone.

The ARVs that are potentially affected by dexamethasone in the doses used for treatment of COVID-19 include rilpivirine, dolutegravir and maraviroc. Since the majority of PLWH currently use integrase inhibitors, the interaction with dexamethasone is only relevant to a small population of patients.

The recommendations in this review are based on experimental and clinical data, extrapolation from other DDIs, potential risk of under- or overdosing and the benefit of the treatment. However, it should be noted that these recommendations do not take into account the inhibitory effect on CYP3A4 in presence of high levels of inflammation as observed for instance in COVID-19 patients.

Also, extrapolation of the inducing CYP3A4 effect from in vitro data considering various dexamethasone dosages is challenging as study methodologies are different with generally small study populations. Thus, future research will need to address the effect of various doses of dexamethasone and treatment durations on ARV exposure both in the presence and absence of high levels of inflammation. Clinical TDM laboratories could join forces to learn more about these DDIs by collecting, sharing and publishing data on ARV plasma concentrations and treatment outcomes in people co-treated with dexamethasone. Furthermore, in vitro to in vivo extrapolation by physiologically based pharmacokinetic modelling can be applied to estimate the impact of various dexamethasone treatment courses on pharmacokinetics of ARVs.

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Author contributions
T.G.J. wrote the first draft of the manuscript; T.G.J., C.M., D.J.B. and D.M.B. added parts of new text and figures; T.G.J. and D.M.B. designed the research; T.G.J. performed the research; T.G.J., C.M., D.J.B. and D.M.B. analysed the data.

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