

APPENDIX E: SIGNIFICANT PHARMACOKINETIC DRUG-DRUG INTERACTIONS FOR DRUGS IN THE TREATMENT OF OIS

This table provides pharmacokinetic drug-drug interaction data between drugs for treatment of OIs and ARV agents. For interactions between drugs for OI treatment and other medications taken by individual patients, consult with other drug information resources.

| DRUGS | INTERACTING WITH | MECHANISM/EFFECTS | RECOMMENDATIONS |
|---|--|---|--|
| Acyclovir | Probenecid (with cidofovir) | Probenecid may ↓ renal clearance of acyclovir by 32% → ↑ acyclovir AUC | No dosage adjustment; monitor for acyclovir toxicities |
| Atovaquone | Rifabutin | Atovaquone conc. ↓ by 34%; rifabutin conc. ↓ by 19% | This combination should be avoided |
| | RIF | Atovaquone conc. ↓ by 52%; RIF conc. ↑ by 37% | This combination should be avoided |
| | Tetracycline | Atovaquone conc. ↓ by 40% | This combination should be avoided ; interaction study with doxycycline not available |
| | AZT | AZT AUC ↑ by 31%, possibly due to atovaquone inhibition of AZT glucuronidation | No dosage adjustment recommended, monitor for AZT toxicities |
| Caspofungin | EFV, NVP, NFV, RIF | Possible ↓ caspofungin conc. based on regression analyses of patient pharmacokinetic data; no formal pharmacokinetic study available at this time | Manufacturer recommended ↑ maintenance dose to 70mg q.d if patient has suboptimal response to caspofungin if co-administered with the interacting drugs |
| Cidofovir (+ Probenecid) | Acyclovir, cephalosporins, dapsone, fluoroquinolones, ganciclovir, penicillins, valacyclovir, valganciclovir, zalcitabine (ddC), AZT | Probenecid may ↓ renal clearance of these drugs → ↑ plasma conc. | Given the infrequent dosing of probenecid when used with cidofovir, no dosage adjustment is necessary for interacting drugs; monitor for dose-related toxicities |
| Ciprofloxacin | Didanosine (ddI)-buffered formulations | ↓ ciprofloxacin absorption due to chelation with magnesium-aluminium buffer | Administer ddI-buffered preparation at least 2 hours after or 6 hours before ciprofloxacin |
| | Cidofovir + probenecid | Probenecid may reduce renal clearance of ciprofloxacin → ↑ plasma conc. | No dosage adjustment necessary; monitor for ciprofloxacin toxicities |
| Clarithromycin CYP 3A4 Inhibitor and Substrate | ATV | ATV C _{min} ↑ 91%; clarithromycin AUC ↑ 94% | Due to concerns of QT prolongation, ↓ clarithromycin dose by 50% or use alternative agent |

| DRUGS | INTERACTING WITH | MECHANISM/EFFECTS | RECOMMENDATIONS |
|--------------------|---------------------------|---|--|
| | DLV | DLV AUC ↑ by 44%; clarithromycin AUC ↑ by 100%; and 14-OH clarithromycin AUC ↓ by 75% | No dosage adjustment recommended; may consider clarithromycin dose adjustment in patients with renal insufficiency; monitor for clarithromycin toxicities; or switch to azithromycin |
| | EFV | Clarithromycin AUC ↓ by 39%; 14-OH clarithromycin AUC ↑ 34% | Significance unknown, no dosage adjustment recommended; some suggest switching to azithromycin |
| | Itraconazole | Possible bi-directional CYP 3A4 inhibition and ↑ AUC of both drugs | Monitor for toxicities of both itraconazole and clarithromycin |
| | LPV/r (Kaletra®) | ↑ clarithromycin AUC and ↓ in 14-OH clarithromycin AUC | No dosage change in patients with normal renal function CrCl (ml/min) clarithromycin 30-60 ↓dose by 50% <30 ↓dose by 75% |
| | Rifabutin | Clarithromycin AUC ↓ by 44%; rifabutin AUC ↑ by 76-99% | May need clarithromycin dose ↑ and ↓ rifabutin dose; may result in ↑ rifabutin toxicities; some suggest to use azithromycin in place of clarithromycin |
| | RIF | ↓ mean clarithromycin conc. by 87% | This combination should be avoided; consider switching to azithromycin |
| | RTV | Clarithromycin AUC ↑ by 77% and ↓ in 14-OH clarithromycin AUC | No dosage change in patients with normal renal function CrCl (ml/min) clarithromycin 30-60 ↓dose by 50% <30 ↓dose by 75% |
| | Trimetrexate | May ↑ trimetrexate AUC | No formal study performed; avoid concomitant use or monitor for trimetrexate toxicities |
| Dapsone | RIF | ↓ dapsone level by 7-10x and ↓ dapsone t1/2 from 24 to 11 hours | Reduced dapsone activities; may consider increasing dapsone dose or use alternative agent |
| Doxycycline | Atovaquone | Tetracycline ↓ atovaquone conc. by 40%; effect of doxycycline on atovaquone unknown | Until doxycycline-atovaquone interaction data become available; avoid this combination if possible |
| | ddI-buffered formulations | ↓ doxycycline absorption due to chelation with magnesium-aluminium buffer | Separate doxycycline with ddI by at least 2 hours or use ddI-enteric-coated capsule |

| DRUGS | INTERACTING WITH | MECHANISM/EFFECTS | RECOMMENDATIONS |
|---|---|---|--|
| | RIF | ↑ doxycycline clearance, ↓ t1/2 and AUC | Potential for ↓ doxycycline efficacy, monitor closely for therapeutic failure |
| Erythromycin CYP 3A4 Inhibitor | Itraconazole | Potential for bi-directional inhibition of hepatic metabolism and ↑ serum conc. of both | Monitor for toxicities of both drugs |
| | Trimetrexate | May ↑ trimetrexate AUC | No formal study performed; avoid concomitant use or monitor for trimetrexate toxicities |
| Fluconazole CYP 3A4 Inhibitor | Rifabutin | Rifabutin AUC ↑ by 80%; no effect on fluconazole levels | Monitor for rifabutin toxicity or may consider dose reduce to 150mg q.d |
| | RIF | Fluconazole AUC ↓ by 23-56%; no change in RIF conc. | May need to ↑ fluconazole dose |
| | Trimetrexate | May ↑ trimetrexate AUC | No formal study performed; avoid concomitant use or monitor for trimetrexate toxicities |
| | AZT | Fluconazole ↓ glucuronidation of AZT; fluconazole 400mg/day results in ↑ AZT AUC by 74% | Monitor for AZT toxicities |
| Ganciclovir | ddI-buffered formulations (study with enteric-coated ddI has not been done) | ddI AUC ↑ by 78% with IV ganciclovir and ↑ by 111% with po ganciclovir | May consider reducing ddI dose; monitor for ddI toxicities |
| | Cidofovir + probenecid | Probenecid may ↓ ganciclovir clearance and ↑ ganciclovir conc. | Given the infrequent dosing of probenecid when used with cidofovir, no dosage adjustment is necessary; monitor for dose-related toxicities |
| Itraconazole CYP 3A4 Inhibitor and Substrate | Clarithromycin | Potential for bidirectional inhibition of CYP3A4 metabolism with ↑ AUC of itraconazole and/or interacting drug(s) | Monitor for toxicities of clarithromycin; monitor itraconazole level and toxicities |
| | DLV | Potential for bidirectional inhibition of CYP3A4 metabolism with ↑ AUC of itraconazole and/or DLV | Monitor for toxicities of DLV; monitor itraconazole level and toxicities |
| | ddI-buffered preparation | May ↓ itraconazole oral absorption due to ↑ gastric pH from antacid in the ddI preparation | Administer itraconazole at least 2-4 hours before ddI-buffered tablets; or use ddI enteric-coated capsule; or take itraconazole with cola beverage to ↓ gastric pH |

| DRUGS | INTERACTING WITH | MECHANISM/EFFECTS | RECOMMENDATIONS |
|---|---------------------------|--|--|
| | EFV | No interaction study reported; potential induction or inhibition of itraconazole metabolism → ↑ or ↓ in itraconazole AUC | Monitor itraconazole level and adjust dose accordingly |
| | Erythromycin | Potential for bidirectional inhibition of CYP3A4 metabolism with ↑ AUC of itraconazole and/or erythromycin | Monitor for toxicities of erythromycin; monitor itraconazole level and toxicities |
| | NVP | Potential for induction of itraconazole metabolism and ↓ in itraconazole conc. | Monitor itraconazole level and adjust according; monitor therapeutic efficacy |
| | PIs other than RTV | Potential for bidirectional inhibition of CYP3A4 metabolism with ↑ AUC of itraconazole and/or PIs | Monitor for toxicities of PIs; monitor itraconazole level and toxicities (esp. in patients with RTV-boosted PI regimens) |
| | Rifabutin | ↓ in itraconazole conc. by 70%; potential for inhibition of rifabutin metabolism and ↑ rifabutin conc. | Avoid concomitant use if possible; if the combination is to be used, monitor itraconazole level and adjust dose accordingly; monitor for rifabutin toxicity |
| | RIF | Itraconazole AUC ↓ by 64%-88%; no change in RIF conc. | Avoid concomitant use if possible; if the combination is to be used, monitor itraconazole level and adjust dose accordingly; monitor therapeutic response |
| | RTV | Potential for significant ↑ in itraconazole conc. | May require reduced itraconazole dose; monitor itraconazole level and toxicities |
| | Trimetrexate | Itraconazole may significantly ↑ trimetrexate level due to inhibition of CYP3A4 metabolism | Monitor for trimetrexate toxicities |
| Ketoconazole CYP 3A4 Substrate | APV | APV AUC ↑ by 31%; ketoconazole AUC ↑ 44% | Monitor for toxicities of each drug |
| | DLV | DLV C _{min} ↑ by 50% | Monitor for DLV toxicities |
| | ddI-buffered formulations | May ↓ oral absorption of ketoconazole due to ↑ gastric pH from antacid in the ddI-preparation | Space apart doses of ketoconazole and ddI by at least 2 hours or administer ketoconazole with cola beverage to ↓ pH |
| | IDV | IDV AUC ↑ by 68%; o significant change in ketoconazole conc. | ↓ IDV dose to 600mg q8h |

| DRUGS | INTERACTING WITH | MECHANISM/EFFECTS | RECOMMENDATIONS |
|--|-------------------------------|---|--|
| | LPV/r (Kaletra [®]) | Ketoconazole AUC ↑ by 3x; no significant change in LPV pharmacokinetics | ↓ ketoconazole dose and monitor for toxicities |
| | NVP | Ketoconazole AUC ↓ by 63%; NPV AUC ↑ by 15%-30% | Consider alternative antifungal or monitor for ketoconazole efficacy |
| | Rifabutin | Possible ↑ in rifabutin conc. and ↓ in ketoconazole conc. | Monitor for rifabutin toxicities and ketoconazole efficacy |
| | RIF | Ketoconazole levels ↓ by 50% | Avoid concomitant use if possible; consider alternative antifungal and/or antimycobacterial agent(s) |
| | RTV | Ketoconazole AUC ↑ by 3.4x | Ketoconazole dose >200mg q.d not recommended; monitor for ketoconazole toxicities |
| | Trimetrexate | Ketoconazole may significantly ↑ trimetrexate level due to inhibition of CYP3A4 metabolism | Monitor for trimetrexate toxicities |
| PZA | AZT | ↓ PZA conc. in one study | Monitor therapeutic efficacy or consider monitoring PZA level |
| Ribavirin | ddI | ↑ intracellular levels of ddA-TP | ↑ ddI-associated mitochondrial toxicities; avoid concomitant use if possible; if used together, monitor for toxicities (lactic acidosis, pancreatitis, peripheral neuropathy) |
| | AZT | ↓ intracellular activities of AZT against HIV <i>in vitro</i> | Potential for worsening of HIV suppression; monitoring HIV viral load |
| Rifabutin CYP 3A4 Inducer and Substrate | APV | Rifabutin AUC ↑ by 193%; no change in APV conc. | ↓ rifabutin dose by 50% (to 150mg q.d) |
| | ATV | Rifabutin AUC ↑ by 210%; C _{min} ↑ by 343%; minimal change in ATV pharmacokinetics | ↓ rifabutin dose by 75% (to 150mg every other day or t.i.w) |
| | Atovaquone | Atovaquone conc. ↓ by 34%; rifabutin conc. ↓ by 19% | This combination should be avoided |
| | Clarithromycin | Rifabutin AUC ↑ by 76% due to inhibition of hepatic metabolism; clarithromycin AUC may be reduced | Consider reducing rifabutin dose, monitor for rifabutin toxicities, or switching macrolide to azithromycin |
| | DLV | DLV AUC ↓ by 80%; rifabutin AUC ↑ by 100% | This combination should be avoided |
| | ddI-buffered formulation | ↓ rifabutin oral absorption | Space rifabutin and ddI-buffered formulation apart by at least 2 hours or use enteric-coated ddI-capsule |

| DRUGS | INTERACTING WITH | MECHANISM/EFFECTS | RECOMMENDATIONS |
|--|------------------|---|--|
| | EFV | Rifabutin AUC ↓ by 38%; no change in EFV conc. | ↑ rifabutin dose to 450 q.d or 600mg b.i.w or t.i.w; effect of EFV + PI(s) on rifabutin conc. has not been studied |
| | Fluconazole | Rifabutin AUC ↑ by 80% due to inhibition of hepatic metabolism | Consider reducing rifabutin dose or monitor for rifabutin toxicities |
| | Fosamprenavir | No data of interaction between fosamprenavir and rifabutin; interaction between APV and rifabutin suggests inhibition of rifabutin metabolism | ↓ rifabutin dose by 50% (to 150mg q.d); if used with RTV/fosamprenavir combination, dose reduction to 150mg q.o.d or t.i.w |
| | Itraconazole | Itraconazole conc. ↓ by 70%; potential for inhibition of rifabutin metabolism and ↑ rifabutin conc. | Avoid concomitant use if possible; if the combination is to be used, monitor itraconazole level and adjust dose accordingly; monitor for rifabutin toxicity |
| | IDV | Rifabutin AUC ↑ by 204%; IDV AUC ↓ by 32% | ↓ rifabutin dose to 150mg q.d and ↑ IDV dose to 1,000mg q8h |
| | Ketoconazole | Possible ↑ in rifabutin conc. and ↓ in ketoconazole conc. | Monitor for rifabutin toxicities and ketoconazole efficacy |
| | LPV/r (Kaletra®) | Rifabutin AUC ↑ by 303%; 25-O-des-acetyl rifabutin AUC ↑ by 47.5x | ↓ rifabutin dose to 150mg every other day or t.i.w |
| | NFV | Rifabutin AUC ↑ by 207%; insignificant Δ in NFV conc. | ↓ rifabutin dose to 150mg q.d |
| | RTV | Rifabutin AUC ↑ by 430%; no change in RTV conc. | ↓ rifabutin dose to 150mg every other day or t.i.w |
| | SQV | SQV AUC ↓ by 43%; no change in rifabutin conc. | This combination should be avoided; may consider adding RTV to SQV and monitor SQV conc. |
| | Voriconazole | Voriconazole AUC ↓ by 79%; rifabutin AUC ↑ by 3x | This combination should be avoided |
| RIF Potent CYP3A4 inducer | APV | APV AUC ↓ by 82%, C _{min} ↓ by 92%; no change in RIF conc. | This combination should be avoided; effect of RIF on RTV + APV has not been studied |
| | ATV | Pharmacokinetic study not available; expect RIF to ↓ ATV concentrations substantially (up to 90%↓), as seen with other PIs | This combination should be avoided |
| | Atovaquone | Atovaquone conc. ↓ by 52%; RIF conc. ↑ by 37% | This combination should be avoided |

| DRUGS | INTERACTING WITH | MECHANISM/EFFECTS | RECOMMENDATIONS |
|-------|------------------|---|--|
| | Clarithromycin | ↓ mean clarithromycin conc. by 87% | This combination should be avoided; consider switching clarithromycin to azithromycin |
| | Dapsone | Dapsone half-life ↓ from 24 to 11 hours; dapsone conc. ↓ by 7-10x | Monitor for dapsone efficacy; consider alternative therapy |
| | DLV | DLV AUC ↓ by 95%, no change in RIF conc. | This combination should be avoided |
| | EFV | EFV AUC ↓ by 22%; no change in RIF conc. | No dosage adjustment or ↑ EFV dose to 800mg q.d |
| | Fluconazole | Fluconazole AUC ↓ by 23%-56%; no change in RIF conc. | May need to ↑ fluconazole dose |
| | Fosamprenavir | No study done with fosamprenavir to date; APV AUC ↓ by 82%, Cmin ↓ by 92% | This combination should be avoided |
| | IDV | IDV AUC ↓ by 89%; RIF conc. slightly ↑ | This combination should be avoided |
| | Itraconazole | Itraconazole AUC ↓ by 64-88%; no change in RIF conc. | Avoid concomitant use if possible; if the combination is to be used, monitor itraconazole level and adjust dose accordingly; monitor therapeutic response |
| | Ketoconazole | Ketoconazole levels ↓ by 50% | Avoid concomitant use if possible; consider alternative antifungal and/or antimycobacterial agent(s) |
| | LPV/r (Kaletra®) | LPV AUC ↓ by 75% and Cmin ↓ by 99%; RIF AUC may be increased | This combination should be avoided |
| | NFV | NFV AUC ↓ 82%; no change in RIF conc. | This combination should be avoided |
| | NVP | NVP AUC ↓ by 37%; no change in RIF conc. | This combination should be used with caution; monitor ARV response |
| | RTV | RTV AUC ↓ by 35%; no change in RIF conc. | Monitor for ARV activity of RTV |
| | SQV | SQV AUC ↓ by 84%; no change in RIF conc. | This combination should be avoided; potential for use in the presence of RTV, consider monitoring SQV concentration |
| | Trimetrexate | May ↑ trimetrexate metabolism and ↓ trimetrexate conc. | Monitor for trimetrexate efficacy |
| | Voriconazole | Voriconazole AUC ↓ by 96% | This combination should be avoided |

| DRUGS | INTERACTING WITH | MECHANISM/EFFECTS | RECOMMENDATIONS |
|--|---|--|--|
| | AZT | RIF ↑ AZT glucuronidation → ↓ AZT AUC by 47% | Monitor for AZT efficacy |
| TDF | Acyclovir, cidofovir, ganciclovir, valacyclovir, valganciclovir | Potential for compete active tubular secretion of these drugs | Monitor for toxicities of these drugs and TDF |
| | ATV | ATV C _{min} ↓ by 40%; mechanism unknown | Co-administer with RTV at a dose of RTV 100mg q.d + ATV 300mg q.d |
| | ddI (buffered and enteric-coated preparations) | ↑ ddI AUC by 44%-60%; no change in TDF AUC | Monitor for ddI-associated toxicities; discontinue ddI if serious toxicity occurs; some suggest reduction of ddI dose (e.g. from 400mg to 250mg in patients >60kg) |
| Trimetrexate CYP 3A4 Substrate | CYP 3A4 inhibitors e.g. clarithromycin, DLV, fluconazole, itraconazole, ketoconazole, voriconazole, PIs | May ↑ trimetrexate concentration | Monitor for trimetrexate toxicities |
| | CYP 3A4 inducers e.g. EFV, NVP, rifabutin, RIF | May ↓ trimetrexate concentration | Monitor for trimetrexate efficacy |
| Valganciclovir | Cidofovir + probenecid | Probenecid may ↓ ganciclovir renal clearance and ↑ ganciclovir conc. | Given the infrequent dosing of probenecid when used with cidofovir, no dosage adjustment is necessary; monitor for dose-related toxicities |
| | ddI-buffered formulation | Oral ganciclovir ↑ ddI AUC by 111% | Monitor for ddI toxicities; study with valganciclovir and ddI enteric-coated formulation has not been done |
| Voriconazole CYP 2C9, 2C19, and 3A4 Substrate and Inhibitor | DLV, EFV | Potential bi-directional inhibition of metabolism → ↑ conc. of both drugs | No formal interaction studies; monitor for toxicities |
| | NVP, EFV | Potential induction of voriconazole metabolism → ↓ voriconazole conc. | No formal interaction studies; monitor for therapeutic failure of voriconazole |
| | PIs (except IDV) | Potential bi-directional inhibition of metabolism → ↑ conc. of both drugs; IDV + voriconazole → no significant interaction | No formal interaction studies except for IDV; monitor for toxicities |
| | Rifabutin | Voriconazole AUC ↓ by 79%; rifabutin AUC ↑ by 3-fold | This combination should be avoided |
| | RIF | Voriconazole AUC ↓ by 96% | This combination should be avoided |

