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Table 21. Drug Interactions Between Antiretrovirals and Other Drugs: PIs, NNRTIs, and NRTIs

Drug Interactions Requiring Dose Modifications or Cautious Use			
Drugs Affected	**Indinavir (IDV)**	**Ritonavir* (RTV)**	**Saquinavir† (SQV)**
ANTIFUNGALS			
Ketoconazole	Levels: IDV ↑ 68%. Dose: IDV 600 mg tid.	Levels: ketoconazole ↑ 3X. Dose: Use with caution; do not exceed 200 mg ketoconazole daily.	Levels: SQV ↑ 3X. Dose: If ketoconazole dose is >200 mg/day, monitor for excessive diarrhea, nausea, abdominal discomfort and adjust doses accordingly.
Voriconazole	Levels: No significant changes in AUC of azole or IDV (healthy subjects). Dose: Standard	No data, but potential for bi-directional inhibition between voriconazole and PIs, monitor for toxicities	No data, but potential for bi-directional inhibition between voriconazole and PIs, monitor for toxicities
ANTI-MYCOBACTERIALS			
Rifampin	Levels: IDV (unboosted) ↓ 89%; IDV (boosted) ↓ 87%; Contraindicated.	Levels: RTV ↓ 35%. Dose: No change. Increased liver toxicity possible. Co-administration may lead to loss of virologic response if RTV sole PI. Alternate antimycobacterial agents, such as rifabutin, should be considered.	Levels: SQV ↓ 84%. Contraindicated, unless using RTV+SQV. Dose: SQV/RTV 400/400 mg BID rifampin 600 mg qd or 3x/week.
Rifabutin	Levels: IDV ↓ 32%. Rifabutin ↑ 2X. Dose: ↓ rifabutin to 150 mg qd or 300 mg 3x/week. IDV 1000 mg tid. If RTV boosted, use rifabutin dosing recommendations for co-administration with RTV; continue current dose of boosted IDV.	Levels: Rifabutin ↑ 4X. Dose: ↓ rifabutin to 150 mg qd or 3x/week.[¢] RTV: Maintain current dose if sole PI or part of a boosted regimen.	Levels: SQV ↓ 40%. Contraindicated unless SQV/RTV. Dose: Rifabutin 150 mg qd or 3x/week.[¢]
Clarithromycin	Levels: Clarithromycin ↑ 53%. No dose adjustment.	Levels: Clarithromycin ↑ 77%. Dose: Adjust clarithromycin dose for moderate and severe renal impairment.	Levels: Clarithromycin ↑ 45%. SQV ↑ 177%. No dose adjustment.
ORAL CONTRACEPTIVES	Levels: Norethindrone ↑ 26%. Ethinylestradiol ↑ 24%. No dose adjustment.	Levels: Ethinyl estradiol ↓ 40%. Use alternative or additional method.	No data.
LIPID–LOWERING AGENTS			
Simvastatin Lovastatin	Levels: Potential for large increase in statin levels. Avoid concomitant use.	Levels: Potential for large increase in statin levels. Avoid concomitant use.	Levels: Potential for large increase in statin levels. Avoid concomitant use.
Atorvastatin	Levels: potential for increase in AUC Use lowest possible starting dose of atorvastatin with careful monitoring.	Levels: 450% ↑ when administered with SQV/RTV combination. Use lowest possible starting dose of atorvastatin with careful monitoring.	Levels: 450% ↑ when administered with SQV/RTV combination. Use lowest possible starting dose of atorvastatin with careful monitoring.
Pravastatin	No Data	Levels: 50% ↓ when administered with SQV/RTV combination. No dose adjustment needed.	Levels: 50% ↓ when administered with SQV/RTV combination. No dose adjustment needed.
ANTICONVULSANTS			
Carbamazepine Phenobarbitol Phenytoin	Carbamazepine markedly ↓ IDV AUC. Consider alternative agent.	Carbamazepine: ↑ serum levels when co-administered with RTV. Use with caution. Monitor anticonvulsant levels.	Unknown, but may markedly ↓ SQV levels. Monitor anticonvulsant levels.
METHADONE	No change in methadone levels.	Methadone ↓ 37%. Monitor and titrate dose if needed. May require ↑ methadone dose.	Methadone AUC ↓ 20%. When co-administered with SQV/RTV 400/400 mg BID. Dose: No adjustment for this PI regimen, but monitor and titrate to methadone response if necessary.
ERECTILE DYSFUNCTION AGENTS			
Sildenafil	Sildenafil AUC ↑ 3 fold. Use cautiously. Start with reduced dose of 25 mg every 48 hours and monitor for adverse effects.	Sildenafil AUC ↑ 11 fold. Use cautiously. Start with reduced dose of 25 mg every 48 hours and monitor for adverse effects.	Sildenafil AUC ↑ 2 fold. Use a 25 mg starting dose of sildenafil.
Vardenafil	Vardenafil AUC ↑ 16 fold. IDV (unboosted) AUC ↓ 30% Dose: Consider Sildenafil instead of vardenafil if IDV unboosted. Do not exceed vardenafil 2.5 mg in 72 hours if administered with RTV.	Vardenafil AUC ↑ 49 fold. RTV AUC ↓ 20% Dose: Vardenafil: Start with a 2.5 mg dose, and do not exceed a single 2.5 mg dose in 72 hours. RTV: Maintain current dose.	No data, but vardenafil AUC may be substantially increased. Start with a 2.5 mg dose and do not exceed a single 2.5 mg dose in 24 hours. Do not exceed a single 2.5 mg dose in 72 hours if administered with RTV.
Tadalafil	Concomitant administration will result in substantial increase in tadalafil AUC and half-life (normal = 17.5h). Start with a 5 mg dose, and do not exceed a single dose of 10 mg every 72 hours.	Tadalafil AUC ↑ 124%. Start with a 5 mg dose, and do not exceed a single dose of 10 mg every 72 hours.	Concomitant administration will result in substantial increase in tadalafil AUC and half-life (normal = 17.5h). Start with a 5 mg dose, and do not exceed a single dose of 10 mg every 72 hours.
MISCELLANEOUS	Grapefruit juice ↓ IDV levels by 26%. Vitamin C >/= 1 gram/day ↓ IDV AUC by 14% and Cmin by 32% Itraconazole: Reduce IDV (unboosted) dose to 600 mg TID; do not exceed 200 mg Itraconazole twice daily. RTV boosted regimen: See RTV.	Many possible interactions Desipramine ↑ 145%, reduce dose Trazadone AUC ↑ 60%. Use lowest dose and monitor for CNS and CV adverse effects. Theophylline ↓ 47%, monitor theophylline levels	Grapefruit juice ↑ SQV levels. Dexamethasone ↓ SQV levels. RTV boosted regimen: See RTV.

* Drugs for which plasma concentrations may be decreased by coadministration with ritonavir: anticoagulants (warfarin), anticonvulsants (phenytoin, divaproex, lamotrigine), antiparasitics (atovaquone).

† Some drug interaction studies were conducted with Invirase®. May not necessarily apply to use with Fortovase.

¢ Rifabutin 3x/week is recommended if CD4 cell count is <100/mm^3

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Table 21. Drug Interactions Between Antiretrovirals and Other Drugs: PIs, NNRTIs, and NRTIs

Drug Interactions Requiring Dose Modifications or Cautious Use			
Drugs Affected	**Nelfinavir (NFV)**	**Amprenavir (APV)**	**Fosamprenavir (fos-APV)**
ANTIFUNGALS			
Ketoconazole	No dose adjustment necessary.	Levels: APV ↑ 31% Keto ↑ 44%. Dose: Standard	Presumably similar interactions (an increase in both APV and Keto levels) and recommendation as APV. Consider keto dose reduction if dose is > 400 mg/day If fos-APV/r: Use with caution; do not exceed 200 mg ketoconazole daily.
Voriconazole	No data, but potential for bi-directional inhibition between voriconazole and PIs exists, monitor for toxicities.	No data, but potential for bi-directional inhibition between voriconazole and PIs exists, monitor for toxicities.	Presumably similar interaction and recommendation as APV.
ANTI-MYCOBACTERIALS			
Rifampin[Σ]	Levels: NFV ↓ 82%. Should not be coadministered.	Levels: APV AUC ↓ 82% No change in rifampin AUC. Should not be coadministered.	Presumably similar interaction and recommendation as APV.
Rifabutin	Levels: NFV ↓32%. Rifabutin ↑ 2X. Dose: ↓ rifabutin to 150 mg qd or 300 mg 3x/week. ↑ NFV dose to 1000 mg tid.	Levels: APV AUC ↓ 15%. Rifabutin ↑ 193%. Dose: No change in APV dose; decrease rifabutin to 150 mg qd or 300 mg 3x/week[ε]. If RTV boosted, use rifabutindosing recommendations for co-administration with RTV; continue current dose of boosted APV.	Similar interaction and recommendation as APV if fos-APV unboosted. If RTV boosted fos-APV, dose reduce rifabtin to 150 mg QOD or 3x/week[ε].
Clarithromycin	No data.	Levels: APV AUC ↑ 18%. No change in clarithromycin AUC. No dose adjustment.	Presumably similar interaction and recommendation as APV.
ORAL CONTRACEPTIVES	Levels: Norethindrone ↓ 18%. Ethinyl estradiol ↓ 47%. Use alternative or additional method.	Levels: ↑ Ethinyl estradiol and norethindrone levels; APV levels ↓ 20%. Do not co-administer; alternative methods of contraception are recommended.	Presumably similar interaction as APV. Do not co-administer; alternative methods of contraception are recommended.
LIPID–LOWERING AGENTS			
Simvastatin **Lovastatin**	Avoid concomitant use. Simvistatin AUC ↑ 505%—not recommended. Potential for large increase in Lovastatin AUC—not recommended.	Levels: Potential for large increase in statin levels. Avoid concomitant use.	Presumably similar interaction and recommendation as APV.
Atorvastatin (ATO)	ATO AUC ↑ 74%–use lowest possible starting dose of atorvastatin with careful monitoring.	ATO levels have potential for large increase. Use lowest possible starting dose of atorvastatin with careful monitoring	ATO AUC ↑ 150%. Maximum ATO dose of 20 mg/day; use with careful monitoring consider alternative agent.
Pravastatin	No data.	No data.	No data.
ANTICONVULSANTS			
Carbamazepine **Phenobarbitol** **Phenytoin**	Unknown, but may decrease NFV levels substantially. Monitor anticonvulsant levels and virologic response. Consider obtaining NFV levels.	Unknown, but may decrease APV levels substantially. Monitor anticonvulsant levels and virologic response. Consider obtaining APV levels.	Presumably similar interaction and recommendation as APV.
METHADONE	NFV may decrease methadone levels, but minimal effect on maintenance dose. Monitor and titrate dose if needed. May require ↑ methadone dose.	Methadone levels ↓ 13%. APV Cmin ↓ 25%. Monitor and titrate methadone if needed.	Presumably similar interaction and recommendation as APV.
ERECTILE DYSFUNCTION AGENTS			
Sildenafil	Sildenafil AUC ↑ 2-11 fold. Use cautiously. Start with reduced dose of 25 mg every 48 hours and monitor for adverse effects.	Sildenafil AUC ↑ 2-11 fold. Use cautiously. Start with reduced dose of 25 mg every 48 hours and monitor for adverse effects.	Similar interaction and recommendations as APV.
Vardenafil	No data, but vardenafil AUC may be substantially increased. Start with a 2.5 mg dose and do not exceed a single 2.5 mg dose in 24 hours. Do not exceed 2.5 mg in 72 hours if administered with RTV.	No data, but vardenafil AUC may be substantially increased. Start with a 2.5 mg dose and do not exceed a single 2.5 mg dose in 24 hours. Do not exceed 2.5 mg in 72 hours if administered with RTV.	Similar interaction and recommendations as APV.
Tadalafil	Concomitant administration will result in substantial increase in tadalafil AUC and half-life (normal=17.5h). Start with a 5 mg dose, and do not exceed a single dose of 10 mg every 72 hours.	Tadalafil half-life = 17.5 hours. Concomitant administration will result in substantial increase in tadalafil AUC and half-life (normal=17.5h). Start with a 5 mg dose, and do not exceed a single dose of 10 mg every 72 hours.	Similar interaction and recommendations as APV.

[ε] Rifabutin 3x/week is recommended if CD4 cell count is <100/mm^3

[Σ] There are limited data on RTV-SQV and LPV-RTV demonstrating that RTV compensates, to a degree, for rifampin induction. In one small study, higher doses of ritonavir (up to 400 mg per dose) or an increased dose of LPV/RTV 800/200 mg were needed to offset rifampin-inducing activity of LPV; the standard dose of rifampin was used in these studies. Of note, 28% of subjects discontinued due to increases in LFTs. The safety of this combination is not established. If co-administered, close monitoring is recommended, as is measuring LPV concentrations.

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Table 21. Drug Interactions Between Antiretrovirals and Other Drugs: PIs, NNRTIs, and NRTIs

Drug Interactions Requiring Dose Modifications or Cautious Use		
Drugs Affected	**Atazanavir (ATV)**	**Lopinavir (LPV)**
ANTIFUNGALS		
Ketoconazole	No dosage adjustment necessary.	Levels: LPV AUC ↓ 13%. Keto ↑ 3-fold. Dose: Use with caution; do not exceed 200 mg ketoconazole daily.
Voriconazole	No data, but potential for bi-directional inhibition between voriconazole and PIs exists; monitor for toxicities.	No data, but potential for bi-directional inhibition between voriconazole and PIs exists, monitor for toxicities.
ANTI-MYCOBACTERIALS		
Rifampin Σ	Should not be coadministered.	Levels: LPV AUC ↓ 75%. Should not be coadministered. A safe and effective dose of LPV/r that can be given with rifampin has not been established.Σ
Rifabutin	Levels: Rifabutin AUC ↑ 2.5-fold Dose: ↓ rifabutin dose to 150 mg qod or 3x/week¢ ATV dose standard.	Levels: Rifabutin AUC ↑ 3-fold. 25-O-desacetyl metabolite ↑ 47.5-fold. Dose: Decrease rifabutin dose to 150 mg QOD or 3x/week; LPV/r: Standard.
Clarithromycin	Levels: clarithromycin AUC ↑ 94% and may cause QTc prolongation. Clarithromycin active metabolite concentrations are significantly reduced Dose: ↓ clarithromycin dose by 50%. Consider alternative therapy.	Levels: ↑ Clarithromycin AUC 77%. Dose: Adjust clarithromycin dose for moderate and severe renal impairment.
ORAL CONTRACEPTIVES	Levels: Ethinyl estradiol AUC ↑ 48%, norethindrone AUC ↑ 110% Dose: use lowest effective dose or alternative methods.	Levels: ethinyl estradiol ↓ 42%. Use alternative or additional method.
LIPID–LOWERING AGENTS		
Simvastatin **Lovastatin**	Levels: Potential for large increase in statin levels. Avoid concomitant use.	Levels: Potential for large increase in statin levels. Avoid concomitant use.
Atorvastatin (ATO)	Atorvastatin levels have potential for large increase. Use lowest possible starting dose of atorvastatin with careful monitoring.	Atorvastatin AUC ↑ 5.88-fold. Use lowest possible starting dose of atorvastatin with careful monitoring.
Pravastatin	No data.	Pravastatin AUC ↑ 33%; no dosage adjustment necessary.
ANTICONVULSANTS		
Carbamazepine **Phenobarbitol** **Phenytoin**	Unknown, but may decrease ATV levels substantially. Monitor anticonvulsant levels.	Many possible interactions: carbamazepine: ↑ levels when co-administered with RTV. Use with caution. Monitor anticonvulsant levels. Phenytoin: ↓ levels of LPV, RTV, and ↓ levels of phenytoin when administered together. Avoid concomitant use.
METHADONE	No data.	Methadone AUC ↓ 53%. Monitor and titrate dose if needed. May require ↑ methadone dose.
ERECTILE DYSFUNCTION AGENTS		
Sildenafil	Sildenafil levels have potential for increase. Start with reduced dose of 25 mg every 48 hours and monitor for adverse effects.	Sildenafil AUC ↑ 11-fold in combination with RTV. Use cautiously. Start with reduced dose of 25 mg every 48 hours and monitor for adverse effects.
Vardenafil	No data, but vardenafil AUC may be substantially increased. Start with a 2.5 mg dose and do not exceed a single 2.5 mg dose in 24 hours. Do not exceed 2.5 mg in 72 hours if administered with RTV.	No data, but vardenafil AUC may be substantially increased. Start with a 2.5 mg dose and do not exceed a single 2.5 mg dose in 72 hours.
Tadalafil	Concomitant administration will result in substantial increase in tadalafil AUC and half-life (normal=17.5h). Start with a 5 mg dose, and do not exceed a single dose of 10 mg every 72 hours.	Tadalafil AUC ↑ 124% when co-administered with RTV. Start with a 5 mg dose, and do not exceed a single dose of 10 mg every 72 hours.
MISCELLANEOUS	Diltiazem AUC ↑ 125%, ↓ diltiazem dose by 50%; ECG monitoring is recommended. Calcium channel blockers: caution is warranted; dose titration should be considered; ECG monitoring is recommended. ATV inhibits UGT and may interfere with irinotecan metabolism; avoid concomitant use. H_2-receptor antagonists: reduced ATV concentrations are expected with simultaneous administration; separate dosing by 12 hours Antacids and buffered medications: reduced ATV concentrations are expected with simultaneous administration; give ATV 2 hr before or 1 hr after these medications RTV boosted regimen: See RTV.	See Also: Miscellaneous RTV recommendations.

Σ There are limited data on RTV-SQV and LPV-RTV demonstrating that RTV compensates, to a degree, for rifampin induction. In one small study, higher doses of ritonavir (up to 400 mg per dose) or an increased dose of LPV/RTV 800/200 mg were needed to offset rifampin-inducing activity of LPV; the standard dose of rifampin was used in these studies. Of note, 28% of subjects discontinued due to increases in LFTs. The safety of this combination is not established. If co-administered, close monitoring is recommended, as is measuring LPV concentrations.

¢ Rifabutin 3x/week is recommended if CD4 cell count is <100/mm^3

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Table 21. Drug Interactions Between Antiretrovirals and Other Drugs: PIs, NNRTIs, and NRTIs

Drug Interactions Requiring Dose Modifications or Cautious Use			
Drugs Affected	**Nevirapine (NVP)**	**Delavirdine (DLV)**	**Efavirenz (EFV)**
ANTIFUNGALS			
Ketoconazole	Levels: Keto. ↓ 63%. NVP ↑ 15-30%. Dose: Not recommended.	No data.	No data.
Voriconazole	No data, but potential for bi-directional interaction between voriconazole and NNRTIs exists; monitor for toxicities and voriconazole effectiveness.	No data, but potential for bi-directional inhibition between voriconazole and delavirdine exists; monitor for toxicities.	No data, but potential for bi-directional interaction between voriconazole and NNRTIs exists; monitor for toxicities and voriconazole effectiveness.
ANTI-MYCOBACTERIALS			
Rifampin	Levels: NVP ↓ 20%-58%. Virologic consequences are uncertain; the potential for additive hepatotoxicity exists. Use of this combination is not recommended; however, if used, coadministration should be done with careful monitoring.	Levels: DLV ↓ 96%. Contraindicated.	Levels: EFV ↓ 25%. Dose: Consider ↑ EFV to 800 mg qd.
Rifabutin	Levels: NVP ↓ 16%. No dose adjustment.*	Levels: DLV ↓ 80%. Rifabutin ↑ 100%. Not recommended.	Levels: EFV unchanged; Rifabutin ↓ 35% Dose: ↑ rifabutin dose to 450-600 mg qd or 600 mg 3x/week.* EFV: Standard
Clarithromycin	Levels: NVP ↑26%. Clarithromycin ↓ 30%. Monitor for efficacy or use alternative agent.	Levels: Clarithromycin ↑100%, DLV ↑ 44%. Dose adjust for renal failure.	Levels: Clarithromycin ↓ 39%. Monitor for efficacy or use alternative agent.
ORAL CONTRACEPTIVES	Levels: ethinyl estradiol ↓ approx 20%. Use alternative or additional methods.	No data.	Levels: Ethinyl estradiol ↑ 37%. No data on other component. Use alternative or additional methods.
LIPID–LOWERING AGENTS			
Simvastatin **Lovastatin**	No data.	Levels: Potential for large increase in statin levels. Avoid concomitant use.	No data.
Pravastatin	No data.	No data.	No data.
ANTICONVULSANTS			
Carbamazepine **Phenobarbitol** **Phenytoin**	Unknown. Use with caution. Monitor anticonvulsant levels.	Unknown, but may decrease DLV levels substantially. Monitor anticonvulsant levels.	Use with caution. Monitor anticonvulsant levels.
METHADONE	Levels: NVP unchanged. Methadone ↓ significantly. Titrate methadone dose to effect.	No data.	Levels: methadone ↓ significantly. Titrate methadone dose to effect.
MISCELLANEOUS	No data.	May increase levels of dapsone, warfarin, and quinidine. Sildenafil: potential for increased concentrations and adverse effects. Use cautiously. Start with reduced dose of 25 mg every 48 hours and monitor for adverse effects. Vardenafil: No data, but vardenafil AUC may be substantially increased. Start with a 2.5 mg dose and do not exceed a single 2.5 mg dose in 24 hours. Tadalafil: No data, but concomitant administration will likely result in substantial increase in tadalafil AUC and half-life (normal=17.5h). Start with a 5 mg dose, and do not exceed a single dose of 10 mg every 72 hours. Atorvastatin levels have potential for large increase. Use lowest possible starting dose of atorvastatin with careful monitoring	Monitor warfarin when used concomitantly.

* These recommendations apply to regimens that do not include PIs, which can substantially increase rifabutin levels.

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Table 21. Drug Interactions Between Antiretrovirals and Other Drugs: PIs, NNRTIs, and NRTIs

Drug Interactions Requiring Dose Modifications or Cautious Use				
Drugs Affected	**Zidovudine (ZDV)**	**Stavudine (d4T)**	**Didanosine (ddI)**	**Tenofovir (TDF)**
METHADONE	No data.	Levels: d4T ↓ 27%, methadone unchanged. No dose adjustment.	Levels: EC ddI unchanged. Buffered ddI AUC ↓ 63%, methadone unchanged. Dose: No change EC ddI. May consider buffered ddI dose increase or maintain standard.	No data.
MISCELLANEOUS				
Ribavirin	Ribavirin inhibits phosphorylation of ZDV; this combination should be avoided if possible or closely monitor virologic response.	No data.	Coadministration not recommended. Ribavirin increases the intracellular levels of the active metabolite of ddI and may cause serious toxicities.	No data.
Didanosine	No data.	Peripheral neuropathy, lactic acidosis, and pancreatitis seen with this combination; use with caution and only if potential benefit outweighs potential risks.	No data.	Levels: ddI AUC ↑ by 44%, Cmax ↑ by 28% Monitor for ddI-associated toxicities For patients > 60 kg, 250 mg/day of ddI EC is recommended.
Atazanavir (ATV)	No data.	No data.	Buffered ddI + ATV simultaneously: Levels: ↓ AUC of ATV 87%; take ATV (with food) 2 hrs before or 1 hr after buffered ddI. No interaction is expected with ddI-EC; however, dosing should be at different times as ATV should be taken with food and ddI-EC on an empty stomach.	ATV 400 + TDF 300 Levels: ATV AUC ↓ 25% and Cmin ↓ by 40%. TDF AUC was ↑ by 24%. Avoid concomitant use. ATV + RTV 300/100 mg qd + TDF 300 mg qd Levels: ATV AUC was ↓ by 25% and Cmin by 23%; ATV Cmin was higher with RTV than ATV without RTV; Consider ATV + RTV (300/100 mg qd) for coadministration with TDF (300 mg qd); however, pharmacokinetic, safety and virologic data are limited.
Indinavir (IDV)	No data.	No data.	Buffered ddI and IDV simultaneously: Levels: ↓ AUC of IDV; take IDV 1 hr before or after buffered ddI.	No data.
Lopinavir/ritonavir	No data.	No data.	No data.	LPV/r 400/100 AUC ↓ 15%; TDF AUC ↑ 34%; clinical significance of interaction is unknown.
Lamivudine plus (Abacavir or Didanosine)	No data.	No data.	No data.	High rate of early virologic non-response with 3TC and ABC plus TDF: combination should be avoided
Cidofovir, Ganciclovir, Valganciclovir	No data.	No data.	ddI + oral ganciclovir (GCV): ddI AUC ↑ 111%; GCV AUC ↓ 21%; Appropriate doses for the combination of ddI and oral GCV have not been established	Possibly competes for active tubular secretion with tenofovir, may increase serum concentration of these drugs and/or tenofovir. Monitor for dose-related toxicities.