

Antiretroviral Interactions With Transplant Medications

	Cyclosporine (Neoral®)	Tacrolimus (Prograf®, Advagraf®) and Sirolimus (Rapamune®)	Mycophenolate Mofetil (CellCept®)
Pharmacokinetic characteristics	>90% metabolized (substrate and inhibitor of CYP3A4; also inhibits P-glycoprotein ¹)	>90% metabolized (substrate of CYP3A4) substrate and inhibitor of P-glycoprotein	MPA, the active metabolite is a substrate of glucuronyl transferase
Integrase Inhibitors			
Raltegravir Metabolized by UGT1A1.	<p>Case report of an HIV-positive liver transplant recipient who received cyclosporine and raltegravir post-transplant. Cyclosporine concentrations were measured regularly and remained therapeutic. Pre- and post dose raltegravir levels were measured at weeks 4 and 8, and were comparable with published data. The authors concluded that raltegravir and cyclosporin may be coadministered without dose adjustment.²</p> <p>In 13 HIV-infected transplant patients (n=8 liver, n=5 kidney) who received raltegravir + 2 NRTIs, median raltegravir C_{trough} was 507 ng/mL (range 176-890) and target C_{trough} of tacrolimus or cyclosporine were achieved with standard doses. After a median follow-up of 9 months (range: 6-14), all patients were alive with satisfactory graft function.³</p>	<p>Raltegravir may avoid interactions with certain immunosuppressives as it is primarily metabolized via glucuronidation and not by CYP3A4.</p> <p>Case report of the successful use of raltegravir/3TC/abacavir and sirolimus in a 49 year old HIV/HCV+ patient who underwent liver transplantation. The patient was switched to this regimen after a series of medication modifications. Pt had developed renal insufficiency with hyperpotasemia and metabolic acidosis due to increased tacrolimus levels (> 25 ng/ml) related to atazanavir use.⁴</p> <p>In 13 HIV-infected transplant patients (n=8 liver, n=5 kidney) who received raltegravir + 2 NRTIs, median raltegravir C_{trough} was 507 ng/mL (range 176-890) and target C_{trough} of tacrolimus or cyclosporine were achieved with standard doses. After a median follow-up of 9 months (range: 6-14), all patients were alive with satisfactory graft function.³</p>	<p>The pharmacokinetics of raltegravir 400 mg BID and mycophenolic acid were prospectively determined in 6 HIV-infected solid-organ transplant recipients. Raltegravir kinetics were not significantly different from historical controls, and MPA metabolism was not significantly altered by raltegravir.⁷</p>

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		<p>In a case series of 11 HIV-positive solid organ transplant (10 liver, 1 renal) patients who received raltegravir/2 NRTI therapy (plus enfuvirtide, n=2) and tacrolimus (91%), median CD4 increased to 380 cells/mm³ and VL remained <50 copies/mL after a median follow-up of 57 weeks. No patients discontinued raltegravir, and no toxicity or interactions with tacrolimus were noted.⁵</p> <p>Two HIV-positive patients began raltegravir-based cART while on tacrolimus 1 or 2 mg twice daily (1 for liver transplantation and 1 for Crohn's disease); no tacrolimus dose adjustment was needed and tacrolimus blood levels were not altered.⁶</p>	
Protease inhibitors			
Amprenavir/ fosamprenavir Primarily metabolized by CYP3A4. Inhibitor of CYP3A4 (similar potency as indinavir and nelfinavir) ⁸ ; also induces CYP3A4 ⁹ .	May ↑/↓ CsA concentrations via CYP3A4 inhibition or induction	May ↑/↓ tacrolimus concentrations via CYP3A4 inhibition or induction. In a case series of HIV-positive patients undergoing liver transplantation, tacrolimus levels were markedly ↑ in the presence of PI-based HAART regimens (LPV/r, APV, and NFV). ¹⁰ In a separate report, a 61-year old patient on fosamprenavir/ritonavir	

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		<p>was started on 0.5 mg QD tacrolimus post-renal transplant; target tacrolimus concentrations were reached within 2 days and tacrolimus was discontinued due to high (37 ng/mL) levels. Target levels were subsequently achieved with tacrolimus 0.5 mg every 4 days.¹¹</p> <p>In four HIV-infected liver transplant patients who switched from nelfinavir to fosamprenavir, mean tacrolimus C_{trough} ↓ significantly from 6.9 to 3.2 ng/mL before vs. after the switch. Tacrolimus dose increase was needed, from an average of 0.29 mg/day to 0.48 mg/day (p=0.046) to attain the desired target of 8.7 +/- 2.3 ng/mL. These findings suggest that fosamprenavir may be less potent than nelfinavir in inhibiting tacrolimus clearance.¹²</p> <p>A retrospective analysis of HIV-positive patients receiving tacrolimus with various cART regimens was conducted. Three liver transplant patients were on ritonavir-boosted PI therapy (1 on saquinavir 1000 mg BID plus lopinavir 400/ritonavir 100 mg BID, 1 on fosamprenavir 700/100 mg BID, 1 on darunavir 600/ritonavir 100 mg BID), and received</p>	

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		<p>tacrolimus doses of 0.06, 0.03, and 0.08 mg daily, with median tacrolimus levels of 6.6, 3.0 and 7.9 ng/mL, respectively. Two other patients began raltegravir-based cART while on tacrolimus 1 or 2 mg twice daily; no tacrolimus dose adjustment was needed and tacrolimus blood levels were not altered.⁶</p> <p>Monitor tacrolimus levels.</p>	
<p>Atazanavir Primarily metabolized by CYP3A4; also inhibits CYP3A.</p>	<p>May ↑ CsA concentrations via CYP3A4 inhibition</p>	<p>May ↑ tacrolimus concentrations via CYP3A4 inhibition.</p> <p>A case report describes a 53-year old HIV-positive, African-American man who received a renal transplant and was placed on mycophenolate mofetil and tacrolimus along with concomitant unboosted atazanavir, abacavir and lamivudine. The patient initially received tacrolimus 0.5 mg on day 2 post-transplant, but serum tacrolimus levels became subtherapeutic by 6 hours, so tacrolimus dosing was changed to 1 mg every 8 hours, and subsequently to 1.5 mg every 12 hours to maintain therapeutic levels and optimize patient convenience.¹³</p> <p>Monitor tacrolimus levels, renal & hepatic function and serum</p>	

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		electrolytes.	
Darunavir Primarily metabolized by CYP3A4; also inhibits CYP3A.	May ↑ CsA concentrations via CYP3A4 inhibition.	<p>May ↑ tacrolimus concentrations via CYP3A4 and/or P-gp inhibition. Case report of a patient with HIV-associated focal segmental glomerulosclerosis who underwent a kidney cadaveric transplantation and was started on a regimen including darunavir/ritonavir. This resulted in a marked increase in tacrolimus trough levels to 106.7 ng/ml (target range 6-7 ng/ml). A decrease in tacrolimus dosage to a single dose of 0.5 mg/week (3.5% of the usual dose) enabled maintenance of stable tacrolimus trough levels.¹⁴</p> <p>A retrospective analysis of HIV-positive patients receiving tacrolimus with various cART regimens was conducted. Three liver transplant patients were on ritonavir-boosted PI therapy (1 on saquinavir 1000 mg BID plus lopinavir 400/ritonavir 100 mg BID, 1 on fosamprenavir 700/100 mg BID, 1 on darunavir 600/ritonavir 100 mg BID), and received tacrolimus doses of 0.06, 0.03, and 0.08 mg daily, with median tacrolimus levels of 6.6, 3.0 and 7.9 ng/mL, respectively. Two other patients began raltegravir-based</p>	

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		cART while on tacrolimus 1 or 2 mg twice daily; no tacrolimus dose adjustment was needed and tacrolimus blood levels were not altered. ⁶	
Indinavir Primarily metabolized by CYP3A4; also an inhibitor of CYP3A4. ¹⁵	May ↑ CsA concentrations via CYP3A4 inhibition. In liver transplant patient (n=1), prolonged t _{1/2} of CsA observed with concomitant IDV/r regimen; daily doses of CsA ↓ 5-20% to maintain serum CsA trough levels. ¹⁶	May ↑ tacrolimus concentrations via CYP3A4 inhibition. In a case series of HIV-positive patients undergoing liver transplantation, tacrolimus levels were markedly ↑ in the presence of PI-based HAART regimens (LPV/r, APV, and NFV) ¹⁰ and IDV, NFV ¹⁷ Monitor tacrolimus levels.	In a small case series (n=6) of HIV+ subjects receiving ddl, 3TC, abacavir, indinavir 800/ ritonavir 100 mg BID and nevirapine 200 mg BID, there was no significant change in indinavir concentrations in the presence of chronic MMF administration. ¹⁸
Lopinavir/ritonavir Lopinavir is primarily metabolized by CYP3A4. Kaletra inhibits CYP3A4, 2D6 (to lesser extent). At clinically relevant concentrations, Kaletra does not inhibit CYP2C9, 2C19, 2E1, 2B6 or 1A2. Induces glucuronyl transferases and possibly CYP1A2 ¹⁹ , CYP2C19 and 2C9. ²⁰	In liver transplant patients (n=2), prolonged t _{1/2} of CsA observed with concomitant LPV/r; daily doses of CsA ↓ 5-20% to maintain serum CsA trough levels. ¹⁶	May ↑ tacrolimus concentrations via CYP3A4 inhibition. In a case series of HIV-positive patients undergoing liver transplantation, tacrolimus levels were markedly ↑ in the presence of PI-based HAART regimens (LPV/r, APV, and NFV). ¹⁰ When a LPV/r based regimen was added to tacrolimus regimen (range 1-6mg BID; target steady state conc: 5-10ng/ml) in 7 HCV-HIV coinfecting liver transplant patients, the tacrolimus dose was reduced by 99% (to 0.5 - 1.5mg every 7- 25 days) to maintain target tacrolimus concentrations. Concentrations of LPV	- may ↓ MMF via GT induction

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		<p>were within the ranges published for patients with normal liver function tests.²¹</p> <p>Similarly, a 41-year old patient on lopinavir/ritonavir was started on 1 mg QD tacrolimus post-renal transplant; target tacrolimus concentrations were reached within 12 hours and the patient was maintained on a dose of 0.5 mg tacrolimus every 8 days.²²</p> <p>A retrospective analysis of HIV-positive patients receiving tacrolimus with various cART regimens was conducted. Three liver transplant patients were on ritonavir-boosted PI therapy (1 on saquinavir 1000 mg BID plus lopinavir 400/ritonavir 100 mg BID, 1 on fosamprenavir 700/100 mg BID, 1 on darunavir 600/ritonavir 100 mg BID), and received tacrolimus doses of 0.06, 0.03, and 0.08 mg daily, with median tacrolimus levels of 6.6, 3.0 and 7.9 ng/mL, respectively. Two other patients began raltegravir-based cART while on tacrolimus 1 or 2 mg twice daily; no tacrolimus dose adjustment was needed and tacrolimus blood levels were not altered.⁶</p> <p>Monitor tacrolimus</p>	

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		levels.	
<p>Nelfinavir Primarily metabolized by CYP3A4; minor pathways include CYP2C19, CYP2D6, others. Inhibitor of CYP3A4.²³</p>	<p>May ↑ CsA concentrations via CYP3A4 inhibition</p>	<p>Case reports of patients undergoing liver transplantation who received nelfinavir; in each instance, tacrolimus concentration rose to toxic levels, and patient developed severe, prolonged tacrolimus toxicity.²⁴ Significant ↓ in nelfinavir dosages (up to >95% ↓) were required.^{24, 25} In a case series of HIV-positive patients undergoing liver transplantation, tacrolimus levels were markedly ↑ in the presence of PI-based HAART regimens (LPV/r, APV, and NFV)¹⁰ and IDV, NFV.¹⁷</p> <p>In a separate case series, 2 HIV-infected liver transplant recipients on NFV + 2 NRTIs experienced ↑ tacrolimus half-life; therapeutic tacrolimus levels were maintained with a 75-93% decrease in the daily dose of tacrolimus. Low NFV concentrations were seen in 1 patient (details not provided).²¹</p> <p>Monitor tacrolimus levels.</p>	<p>- may decrease MMF via GT induction</p>
<p>Ritonavir Potent inhibitor of CYP enzymes in following order: 3A>2D6>2C9>2C19>> 2A6>2E1. Induces glucuronyl transferases and CYP1A2.¹⁵ May also induce CYP2C9,</p>	<p>Low dose ritonavir (as booster) shown to ↑ t_{1/2} of CsA in liver-transplant patients (n=3); daily doses of CsA ↓ 5-20% to maintain serum CsA trough levels.¹⁶</p>	<p>Case report of HCV/HIV patient who underwent liver transplantation; patient received saquinavir, ritonavir, and nelfinavir at various times with tacrolimus. In each instance, tacrolimus concentration</p>	<p>- may decrease MMF via GT induction</p>

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2C19.		rose to toxic levels, and patient developed severe, prolonged tacrolimus toxicity. ²⁵ Monitor tacrolimus concentrations and adjust dosage accordingly.	
Saquinavir Primarily metabolized by CYP3A4. Weak inhibitor of CYP3A4. ¹⁵	Case report of an HIV-positive renal transplant patient whose cyclosporine levels tripled 3 days after initiation of SQV; postulated mechanism was competition for CYP3A metabolism and P-glycoprotein drug transport by SQV. ²⁶	<p>Case report of HCV/HIV patient who underwent liver transplantation; patient received saquinavir, ritonavir, and nelfinavir at various times with tacrolimus. In each instance, tacrolimus concentration rose to toxic levels, and patient developed severe, prolonged tacrolimus toxicity.²⁵</p> <p>A retrospective analysis of HIV-positive patients receiving tacrolimus with various cART regimens was conducted. Three liver transplant patients were on ritonavir-boosted PI therapy (1 on saquinavir 1000 mg BID plus lopinavir 400/ritonavir 100 mg BID, 1 on fosamprenavir 700/100 mg BID, 1 on darunavir 600/ritonavir 100 mg BID), and received tacrolimus doses of 0.06, 0.03, and 0.08 mg daily, with median tacrolimus levels of 6.6, 3.0 and 7.9 ng/mL, respectively. Two other patients began raltegravir-based cART while on tacrolimus 1 or 2 mg twice daily; no tacrolimus dose adjustment was needed and tacrolimus blood</p>	

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		levels were not altered. ⁶ Monitor tacrolimus concentrations and adjust dosage accordingly.	
NNRTIs			
Efavirenz induces CYP3A4 and inhibits 2C9, 2C19, and 3A4 isoenzymes ³	54% ↓ in CsA concentrations observed in renal-transplant patient 5 days after initiating efavirenz regimen. ²⁷	In a case series of HIV-positive patients undergoing liver transplantation, tacrolimus levels were markedly ↓ in the presence of EFV-based HAART regimens. ¹⁰ When an EFV based regimen was added to tacrolimus in 4 HCV-HIV coinfecting liver transplant patients, very little change in tacrolimus dosing was required. ²¹ Concentrations of EFV were within the ranges published for patients with normal liver function tests. Monitor tacrolimus concentrations and adjust dosage accordingly.	
Nevirapine Potent inducer of CYP3A4 and 2B6 enzymes. ²	May ↓ CsA concentrations via CYP3A induction	May ↓ tacrolimus concentrations via CYP3A induction. In a case series of HIV-positive patients undergoing liver transplantation, no changes in tacrolimus levels were observed in patients on nevirapine, Trizivir, or tenofovir. ¹⁰	In a small case series (n=6) of HIV+ subjects receiving ddI, 3TC, abacavir, indinavir 800/ritonavir 100 mg BID and nevirapine 200 mg BID, NVP clearance ↑ 27% in the presence of chronic MMF administration. Clinical significance unclear. ¹⁸
NRTIs			
Tenofovir		In a case series of HIV-positive patients undergoing liver transplantation, no changes in tacrolimus levels were observed in patients on nevirapine,	

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		Trizivir, or tenofovir. ¹⁰ When TDF/3TC/ddI were added to tacrolimus in 1 HCV-HIV coinfecting liver transplant patient, very little change in tacrolimus dosing was required. ²¹	
Zidovudine		In a case series of HIV-positive patients undergoing liver transplantation, no changes in tacrolimus levels were observed in patients on nevirapine, Trizivir, or tenofovir. ¹⁰	Zidovudine - both are substrates of glucuronyl transferase; competitive inhibition may result in ↑AZT or MPA

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