

Antiretroviral Interactions with Transplant Medications

	Cyclosporine	Tacrolimus (and Sirolimus)	Mycophenolate Mofetil
Pharmacokinetic characteristics	>90% metabolized (substrate of CYP3A4); substrate and inhibitor of P-glycoprotein ¹	>90% metabolized (substrate of CYP3A4) substrate and inhibitor of P-glycoprotein	MPA, the active metabolite is a substrate of glucuronyl transferase
Protease inhibitors			
Amprenavir/ fosamprenavir Primarily metabolized by CYP3A4. Inhibitor of CYP3A4 (similar potency as indinavir and nelfinavir) ² ; also induces CYP3A4 ³ .	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). ⁴ In a separate report, a 61-year old patient on fosamprenavir/ritonavir 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. ⁵ Monitor tacrolimus levels.	
Atazanavir Primarily metabolized by CYP3A4; also inhibits CYP3A.	May ↑ CsA concentrations via CYP3A4 inhibition	May ↑ tacrolimus concentrations via CYP3A4 inhibition. Monitor tacrolimus levels, renal & hepatic function and serum electrolytes.	
Indinavir Primarily metabolized by CYP3A4; also an inhibitor of CYP3A4. ⁶	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. ⁷	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) ⁴ and IDV, NFV ⁸ Monitor tacrolimus levels.	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, there was no significant change in indinavir concentrations in the presence of chronic MMF administration. ⁹
Lopinavir/ritonavir	In liver transplant patients	May ↑ tacrolimus	- may ↓ MMF via GT

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<p>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 CYP1A2¹⁰, CYP2C19 and 2C9.¹¹</p>	<p>(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.⁷</p>	<p>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).⁴ In a separate case series, 3 HIV-infected liver transplant recipients on LPV/r + 2 NRTIs experienced significant ↑ tacrolimus half-life; therapeutic tacrolimus levels were maintained when tacrolimus dosing was reduced to once every 5-10 days.¹² 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.⁵</p> <p>Monitor tacrolimus levels.</p>	<p>induction</p>
<p>Nelfinavir Primarily metabolized by CYP3A4; minor pathways include CYP2C19, CYP2D6, others. Inhibitor of CYP3A4.¹³</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.¹⁴ Significant ↓ in nelfinavir dosages (up to >95% ↓) were required.^{14, 15}</p> <p>In a case series of HIV-positive patients undergoing liver transplantation, tacrolimus levels were markedly ↑ in</p>	<p>- may decrease MMF via GT induction</p>

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		<p>the presence of PI-based HAART regimens (LPV/r, APV, and NFV)⁴ and IDV, NFV.⁸</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 when tacrolimus was dosed once every 24 hours.¹²</p> <p>Monitor tacrolimus levels.</p>	
<p>Ritonavir Potent inhibitor of CYP enzymes in following order: 3A>2D6>2C9>2C19>>2A6>2E1. Induces glucuronyl transferases and CYP1A2.⁶ May also induce CYP2C9, 2C19.</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.⁷</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 rose to toxic levels, and patient developed severe, prolonged tacrolimus toxicity.¹⁵ Monitor tacrolimus concentrations and adjust dosage accordingly.</p>	<p>- may decrease MMF via GT induction</p>
<p>Saquinavir Primarily metabolized by CYP3A4. Weak inhibitor of CYP3A4.⁶</p>	<p>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.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 rose to toxic levels, and patient developed severe, prolonged tacrolimus toxicity.¹⁵ Monitor tacrolimus concentrations and adjust dosage accordingly.</p>	
NNRTIs			
<p>Efavirenz induces CYP3A4 and inhibits 2C9, 2C19, and 3A4 isoenzymes³</p>	<p>54% ↓ in CsA concentrations observed in renal-transplant patient 5 days after initiating</p>	<p>In a case series of HIV-positive patients undergoing liver transplantation, tacrolimus</p>	

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	efavirenz regimen. ¹⁷	levels were markedly ↓ in the presence of EFV-based HAART regimens. ⁴ In a separate case series, 2 HIV-infected liver transplant recipients on EFV + 2 NRTIs did not experience significant changes in tacrolimus half-life or oral clearance, and tacrolimus dosage adjustment was not required. ¹² 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. ⁴	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. ⁹
NRTIs			
Tenofovir		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. ⁴	
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. ⁴	Zidovudine - both are substrates of glucuronyl transferase; competitive inhibition may result in ↑AZT or MPA

References:

1. Novartis Pharmaceuticals. Neoral Product Monograph. 2001
2. GlaxoSmithKline. Agenerase (amprenavir) Prescribing Information. Research Triangle Park, NC: October 2002
3. GlaxoSmithKline. Lexiva (fosamprenavir) Prescribing Information. Research Triangle Park, NC: October 2003
4. Neff G, Tzakes A, Safdar K, Jayaweera D. Liver transplantation in HIV, complex pharmacokinetic

- interactions between tacrolimus and highly active antiretroviral therapy [abstract 8.4]. 4th International Workshop on Clinical Pharmacology of HIV Therapy, Cannes, France. March 27-29, 2003:34.
5. Barrail-Tran A, Furlan V, Blouin P, Creput C, Durrbach A, Taburet A. Effect of coadministered protease inhibitor regimen on tacrolimus blood concentration in 3 kidney transplanted HIV-infected patients [abstract 58]. 8th International Workshop on Clinical Pharmacology of HIV Therapy, Budapest, Hungary. April 16-18, 2007.
 6. Eagling VA, Back DJ, Barry MG. Differential inhibition of cytochrome P450 isoforms by the protease inhibitors, ritonavir, saquinavir and indinavir. *Br J Clin Pharmacol* 1997;44:190-4.
 7. Vogel M, Voight E, Wasmuth JC, Michaelis HC, Sudhop T, Schafer N, et al. Drug to drug interactions between ritonavir and cyclosporine A in liver-transplanted HIV-infected patients [abstract]. 5th International Workshop on Clinical Pharmacology of HIV Therapy, Rome, Italy. April 1-3, 2004.
 8. Jain AK, Venkataramanan R, Shapiro R, Scantlebury VP, Potdar S, Bonham CA, et al. The interaction between antiretroviral agents and tacrolimus in liver and kidney transplant patients. *Liver Transplantation* 2002;8:841-5.
 9. Martorell J, Brunet M, García F, Mestre G, Plana M, Libois A, et al. Mycophenolate mofetil lowers plasma nevirapine concentrations but has no effect on intracellular triphosphate concentrations [abstract 539]. 10th Conference on Retroviruses and Opportunistic Infections, Boston, MA. February 10-14, 2003.
 10. Abbott Laboratories. Kaletra Product Monograph. North Chicago: September 2000
 11. Yeh R, Gaver V, Park JJ, Patterson K, Rezk N, Baxter-Meheux F, et al. Lopinavir/ritonavir induces CYP2C9 and 2C19 activity, as measured by warfarin and omeprazole biomarkers in healthy human volunteers [abstract 4.1]. 5th International Workshop on Clinical Pharmacology of HIV Therapy, Rome, Italy. April 1-3, 2004.
 12. Faivre L, Teicher H, Vincent I, Abbara C, Samuel D, Duclos-Vallee J, et al. Potent drug interactions between tacrolimus and lopinavir/ritonavir therapy in HIV-infected liver transplant recipients [abstract 26]. 6th International Workshop on Clinical Pharmacology of HIV Therapy, Quebec. April 28-30, 2005:19.
 13. Lee CA, Liang BH, Wu EY, Grettenberger HM, Sandoval TM, Zhang KE, et al. Prediction of nelfinavir mesylate (VIRACEPT) clinical drug interactions based on in vitro human P450 metabolism studies. 4th National Conference on Retroviruses and Opportunistic Infections, Washington DC. January 22-26, 1997.
 14. Schvarcz R, Rudbeck G, Soderdahl G, et al. Interaction between nelfinavir and tacrolimus after orthoptic liver transplantation in a patient coinfectd with HIV and hepatitis C virus (HCV). *Transplantation* 2000;69:2194-5.
 15. Sheikh AM, Wolf DC, Lebovics E, Goldberg R, Horowitz H. Concomitant human immunodeficiency virus protease inhibitor therapy markedly reduces tacrolimus metabolism and increases blood levels. *Transplantation* 1999;68:307-9.
 16. Brinkman K, Huysmans F, Burger DM. Pharmacokinetic interaction between saquinavir and cyclosporine [letter]. *Ann Intern Med* 1998;129:915-6.
 17. Tseng A, Nguyen ME, Cardella C, Humar A, Conly J. Probable interaction between efavirenz and cyclosporine. *AIDS* 2002;16:505-506.