DRUG INTERACTIONS WITH NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS

	Abacavir (ABC) Ziagen®[1]	**Zidovudine (AZT) Retrovir® [2]**	**Lamivudine (3TC) 3TC®[3]**	**Didanosine (ddI) Videx®, Videx EC®[4]**	**Zalcitabine (ddC) Hivid®[5]**	**Stavudine (d4T) Zerit®[6]**
Usual Dose	300 mg po BID	200 mg po q8h (TID), or 300 mg po BID	150 mg po BID or 300 mg once daily	*Buffered tablets (ddI-BT):* >60 kg = 200 mg po q12h or 400mg QD; <60 kg = 125 mg po BID or 250mg QD *Enteric capsule (ddI-EC):* > 60kg =400mg q24h; <60kg = 250mg q24h	0.75 mg po TID	>60 kg: 20-40 mg po BID <60 kg: 15-30 mg po BID
Kinetic Characteristics	18% CSF penetration; hepatic metabolism via alcohol dehydrogenase and glucuronidation pathways.	15-135% (average 60%) CSF penetration; first pass metabolism, hepatic glucuronidation; 14% (parent) and 75% (metabolite) renal elimination.	10% CSF penetration; 70% renal elimination.	Requires basic media for absorption (tablet contains Mg/ Ca buffers); 21% CSF penetration; partially metabolized via hypoxanthine; 30-50% renal elimination.	15-20% CSF penetration; 62-75% renal elimination.	16-72% (average 30%) CSF penetration; not metabolized; 34-43% renal elimination.
Food	Can take with or without food.[7]	Best on an empty stomach. Can take with a non-fatty meal to minimize nausea. Fatty foods result in a 57% ↓ in AZT concentrations.[8]	Can take with or without food. Diabetics should be warned that the solution contains 20g/100ml of sucrose. Solution is now alcohol-free.	*Buffered tablets (ddI-BT):* ddI AUC ↓ 47% with food; take on empty stomach (30min before or 2 hours after meals). *Enteric capsule (ddI-EC):*	Best on an empty stomach, but can take with or without food.	Can take with or without food.

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				Reductions in ddI Cmax and AUC [9]): • High fat meal (↓ 46%, 19%) • Light meal (↓ 22%, 27%) • 1.5 hours before a light meal (15%, 24%) • 2 hours after a light meal (15%, 10%) • with yogurt: (30%, 20%) • with applesauce: (24%, 18%) **Administer 1.5 hours before or 2 hours after food.**		
Acyclovir		Case report of profound lethargy.[10] No drug interaction seen in larger study.[11]				
Alcohol	No disulfiram reaction noted, no change in EtOH PK, 41% ↑ ABC AUC (not clinically significant).[12]					

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Allopurinol			`	122% ↑ ddI AUC, 116% ↑ Cmax in healthy subjects. Clinical significance unclear[13] Allopurionol 300mg/day + ddI buffered tabs 200mg/day resulted in similar ddI AUC as ddI 200mg BID.[14] **Combination is contraindicated** based on the ↑ potential for ddI-associated toxicity due to increase in didanosine levels.[4]		
Amprenavir (APV)	29% ↑ APV AUC. No change in ABC concentrations.[15] Synergistic activity in vitro.[16]	31% ↑ AZT AUC. 13% ↑ APV AUC No dosage adjustment is required.[17]	No significant interaction.[17]	No significant changes in amprenavir AUC or Cmin observed when administered: concurrently with ddI-EC (in fasting state) concurrently with ddI tablets (in fasting state) 1 hour prior to		

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				ddI tablets (fasting) compared to amprenavir alone in the fasting state. Authors suggest amprenavir may be dosed concurrently with both ddI tablets and enteric-coated capsules in the fasting state.[18]		
Antacids				May ↑ ddI levels. Additive antacid side-effects (i.e. diarrhea).[4]	25% ↓ ddC levels. Space out by 2 hours.[5]	
Antineoplastics, flucytosine, trimetrexate		Increased hematotoxicity. No significant kinetic interaction with antineoplastics.[19]		Additive neuropathy with vinca alkaloids.	Additive neuropathy with vinca alkaloids.	Additive neuropathy with vinca alkaloids.
Atazanavir		In healthy volunteers (n=20), atazanavir 400 mg daily plus Combivir BID at steady-state did not result in any significant changes to PK parameters of any drug.[20] Atazanavir may be	In healthy volunteers (n=20), atazanavir 400 mg daily plus Combivir BID at steady-state did not result in any significant changes to PK parameters of any drug.[20] Atazanavir may be	Simultaneous administration of atazanavir, ***didanosine tablets*** and stavudine resulted in 89% ↓ Cmax and 87% ↓ AUC of atazanavir; kinetics of didanosine and		Simultaneous administration of atazanavir, didanosine tablets and **stavudine** resulted in 89% ↓ Cmax and 87% ↓ AUC of atazanavir (likely due to buffer in ddI tablets); kinetics of

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		coadministered with zidovudine and lamivudine without dosage adjustment.	coadministered with zidovudine and lamivudine without dosage adjustment.	stavudine were not affected. When atazanavir was administered 1 hour apart from didanosine, atazanavir concentrations were not affected. Recommend taking ddI-tablets 30 minutes before or 2 hours after atazanavir (which is taken with food).[21] ***ddI-EC*** should be given 1.5 hours before or 2 hours after atazanavir (which is taken with food).		didanosine and stavudine were not affected.[21] No dosage adjustment required for simultaneous administration of d4T and atazanavir.
Atovaquone		35% ↑ AZT AUC. No dosage adjustment recommended. Monitor for AZT toxicity.[22]				
Azithromycin		10% ↑ in AZT AUC. No dosage adjustment recommended.[23]				
Cimetidine		Inhibition of AZT clearance,		May ↑ ddI levels. Monitor for ddI	36% ↑ ddC AUC. Give ddC 2 hours	

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		however dosage adjustment not warranted.[24]		toxicity.	before cimetidine, or use sucralfate instead.[5]	
Clarithromycin		10-25% ↓ AZT AUC. Consider spacing out administration by 2 hours. Monitor for AZT efficacy.[25]				
Dapsone		↑ hematotoxicity; dapsone induced methemoglobinemia in mouse model.[26]		Early reports of dapsone failure,[27], however no kinetic interaction.[28] Spacing of doses is not required. Additive neuropathy.	20% ↓ dapsone clearance.[29] Additive neuropathy.	Additive neuropathy.
Darunavir	No drug interaction expected, based on different elimination pathways (i.e., renal excretion) of NRTIs.[30]	No drug interaction expected, based on different elimination pathways (i.e., renal excretion) of NRTIs.[30]	No drug interaction expected, based on different elimination pathways (i.e., renal excretion) of NRTIs.[30]	In healthy volunteers, didanosine 400 mg QD on an empty stomach and darunavir 600 mg/ritonavir 100 mg BID with food (2 hours after ddI intake) did not significantly affect plasma levels of either drug. No dosage adjustment is required.[31]	No drug interaction expected, based on different elimination pathways (i.e., renal excretion) of NRTIs.[30]	No drug interaction expected, based on different elimination pathways (i.e., renal excretion) of NRTIs.[30]
Delavirdine		No kinetic		37% ↓ DLV AUC		

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(DLV)		interaction.[32] Additive-synergistic effect in vitro with combination.[32]		and 22% ↓ ddI AUC. Give DLV 1 hour before ddI if possible.[32, 33]		
Didanosine (ddI)		19% ↓ ddI AUC; 35% ↑ AZT AUC. No dosage adjustments required. [34] Another study showed no interaction.[35]			Additive toxicities. **Avoid combination**.[5, 36]	No kinetic interaction.[37] Additive neuropathy.
Efavirenz	No significant interaction.[38]	No significant interaction.[39]	No significant interaction. [39]	EFV does not interact with antacids, therefore ddI buffer should not interfere with EFV absorption.[39]		
Elvitegravir (GS-9137)	In healthy subjects, elvitegravir 200 mg/ritonavir 100 mg QD did not have significant effects on the kinetics of single dose abacavir, and vice versa. No dose adjustments of elvitegravir are required.[40]	In healthy subjects, elvitegravir 200 mg/ritonavir 100 mg QD did not have significant effects on the kinetics of multi-dose zidovudine, and vice versa. No dose adjustments of elvitegravir are required.[40]	No clinically relevant drug interaction observed when healthy subjects (n=24) received elvitegravir 50 mg/rtv 100 mg QD with or without **emtricitabine 200 mg/tenofovir 300 mg QD**.[41] As such, no significant	In healthy subjects, elvitegravir 200 mg/ritonavir 100 mg QD plus single dose didanosine resulted in 14% ↓ AUC and 25% ↓ Cmin of didanosine, while elvitegravir exposure was not significantly altered. No dose adjustments of		In healthy subjects, elvitegravir 200 mg/ritonavir 100 mg QD did not have significant effects on the kinetics of single dose stavudine and vice versa. No dose adjustments of elvitegravir are required.[40]

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			interaction is expected between lamivudine and elvitegravir/ ritonavir.	elvitegravir are required.[40]		
Emtricitabine (FTC)		Prospective, single-dose kinetic study in healthy volunteers of 200 mg FTC plus 300 mg zidovudine resulted in 26% ↑ AUC and 66% ↑ Cmax of zidovudine. FTC kinetics were unchanged. Clinical significance unknown, but dosage adjustments may not be needed.[42]				Prospective, single-dose kinetic study in healthy volunteers of 200 mg FTC plus 40 mg stavudine resulted in no change in kinetics of either drug. Dosage adjustments not required.[42]
Fexofenadine				May ↓ fexofenadine absorption. Give fexofenadine 2 hours before or after ddI.[43]		
Foscarnet		Increased risk of anemia.[44]				
Fluconazole		74% ↑ AZT AUC. Monitor for AZT		No kinetic interaction with		No kinetic

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		toxicity.[45]		either ddI-BT or ddI-EC.[46, 47]		interaction.[48]
Ganciclovir (GCV) *see also Valganciclovir		Additive hematotoxicity which can be serious. Best to avoid combination, or use lower doses of AZT during GCV induction therapy.[49] PO GCV: 19.5% ↑ AZT AUC; no change in GCV AUC.[50]		PO GCV: >100% ↑ ddI AUC and 23% ↓ ganciclovir AUC (*if ddI given 2 hours before GCV*) & no effect on GCV AUC (*ddI given at same time as GCV*). Consider administration of PO GCV at the same time as ddI.[50, 51] IV GCV: >70% ↑ ddI AUC.[52] For both IV and PO GCV, monitor for ddI toxicity (pancreatitis, neuropathy).[4] Mechanism possibly related to phosphorylated GCV metabolite inhibition of purine nucleoside phosphorylase enzyme (PNP), which is responsible for ddI breakdown.[53]		

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Indinavir (IDV)	No significant interaction.[38]	13% ↑ IDV AUC; 17% ↑ AZT AUC. No dosage adjustment is required.[54]		84% ↓ IDV AUC. Administer indinavir ≥ 1 hour prior to ddI-BT.[55, 56] Enteric coated formulation of didanosine (ddI-EC) may be coadministered with indinavir.[9]		25% ↑ d4T AUC. Monitor for d4T toxicity.[54] Prospective study in healthy volunteers of d4T 40 mg single plus indinavir 800mg resulted in no significant changes in d4T AUC or Cmax. When d4T was coadministered with indinavir 800 mg/ritonavir 200 mg, d4T Cmax was unchanged, while d4T AUC ↑ 24%; this was not felt to be clinically significant, and no dosage adjustments are recommended.[57]
Itraconazole		No significant interaction.[58]		Undetectable itraconazole levels (capsules only). Give itraconazole 2 hours before or after ddI-BT.[59] No change in itraconazole		

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				concentration when co-administered with ddI-EC.[47]		
Ketoconazole				May reduce ketoconazole levels. Give ketoconazole 2 hours before or after ddI.[56] Enteric coated formulation of didanosine (ddI-EC) may be coadministered with ketoconazole.[9]		
Lamivudine (3TC)	15% ↓ 3TC AUC. No change in ABC levels.[60]	No significant kinetic interaction.[3] Case reports of profound anemia with combination.[61, 62] 3TC may resensitize AZT to HIV.[63]			Antagonism. **Avoid combination.**[64]	No kinetic interaction.[6]
Lopinavir/ ritonavir						
Maraviroc		Maraviroc had no effect on the pharmacokinetics of zidovudine.[65]	Maraviroc had no effect on the pharmacokinetics of lamivudine.[65]			
Methadone	↓ ABC Cmax, ↑ Tmax, likely not	41% ↑ AZT levels. Monitor for AZT		41% ↓ ddI AUC. Significance of		27% ↓ d4T AUC. Significance of

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(oral) Other opioid dependence therapies LAAM (l-alpha-acetylmethadol), buprenorphine, naltrexone	clinically significant; minor ↑ methadone clearance with ABC.[66]	toxicity.[67] No significant interaction seen with LAAM (l-alpha-acetylmethadol), buprenorphine, naltrexone.[68]		interaction unknown.[69] Analysis of methadone's effect on ddI exposure showed that ddI Cmax and AUC ↓ less than 20% with the enteric coated capsules, while ddI Cmax ↓ 40% and AUC ↓ 30% when given as buffered tablets. Since formulation characteristics for the pediatric powder and the buffered tablet are similar, **do not coadminister methadone with ddI pediatric powde**r due to significant ↓ in ddI concentrations. If coadministration of methadone and didanosine is necessary, use ddI EC formulation and monitor for HIV clinical		interaction unknown, but may require higher doses of d4T.[69]

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				response.[4]		
Mycophenolate mofetil (MMF) *(active metabolite, mycophenolic acid: GT)*			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 intracellular abacavir TP concentrations in the presence of chronic MMF administration.[70]	MMF absorption may be decreased in the presence of antacids containing magnesium and aluminum. Administer MMF at least 1 hour prior or 2 hours after ddI buffered tablets.		
Nelfinavir		35% ↓ AZT AUC. Monitor for AZT efficacy.[71]	10%↑ 3TC AUC.[71]	No interaction, however NFV should be given with food, and ddI on an empty stomach.[71]		No significant interaction.[71]
Nevirapine (NVP)		32% ↓ AZT AUC. Monitor for AZT efficacy. [72]	No significant interaction.[73]	No significant interaction.[74, 75]	No significant interaction.[74, 75]	
NSAIDS (i.e. naproxen, indomethacin)		Neither indomethacin nor naproxen significantly affect AZT levels.[76, 77]				
Pentamidine		Increased hematotoxicity.	Additive pancreatoxicity.	Additive pancreatoxicity. Due to prolonged	Additive pancreatoxicity. Due to prolonged	Additive pancreatoxicity. Due to prolonged

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				half-life of pentamidine, do not restart didanosine until one week after pentamidine therapy is concluded.[78] Monitor amylase, lipase monthly. **Avoid combination if possible**	half-life of pentamidine, do not restart zalcitabine until one week after pentamidine therapy is concluded.[78] Monitor amylase, lipase monthly. **Avoid combination if possible**	half-life of pentamidine, do not restart stavudine until one week after pentamidine therapy is concluded.[78] Monitor amylase, lipase monthly. **Avoid combination if possible**
Phenytoin		30% ↓ AZT clearance. Monitor for AZT toxicity.[2]				
Probenecid		80% ↑ AZT AUC. Consider reducing AZT dosage. Monitor for AZT toxicity, rash, and flu-like symptoms.[79]			50% ↑ ddC AUC. Monitor for ddC toxicity. May require ddC dose reduction.[5]	
Pyrazinamide (PZA)		Potential ↓PZA AUC and efficacy. Clinical significance unknown.[80]				
Quinolones (ciprofloxacin, gatifloxacin, levofloxacin, moxifloxacin)				98% ↓ ciprofloxacin AUC. Give ciprofloxacin 2 hours before or 6 hours after ddI.[81, 82] Enteric		

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				coated formulation of didanosine (ddI-EC) may be co-administered with ciprofloxacin.[9]		
Ribavirin	Ribavirin is a guanosine analogue. Theoretically, ribavirin and abacavir may compete for intracellular phosphorylation, possibly reducing anti-HCV activity of ribavirin. Some controversy exists whether concomitant abacavir therapy may be associated with a reduced response to pegylated interferon and ribavirin,[83-85] but a recent in vitro study showed that the anti-HCV activity of ribavirin was not modified by abacavir[86].	In vitro, ribavirin may antagonize AZT via competition for phosphorylation.[91] In vivo, a case series failed to show increased viral loads with patients on HAART, suggesting that AZT may be used with ribavirin.[92] In a prospective kinetic study, ribavirin 800 mg/daily did not affect the intracellular phosphorylation or plasma kinetics of ZDV, 3TC, or d4T in HCV/HIV-co-infected patients when assessed after 8-12 weeks of co-administration.[93]	In a prospective kinetic study, ribavirin 800 mg/daily did not affect the intracellular phosphorylation or plasma kinetics of ZDV, 3TC, or d4T in HCV/HIV-co-infected patients when assessed after 8-12 weeks of co-administration.[93]	*In vitro,* ribavirin ↑ levels of active ddI metabolite, dideoxyadenosine 5'-triphosphate (ddATP). Potential for ↑ mitochondrial toxicity (i.e. pancreatitis, hyperlactatemia, fatal lactic acidosis, peripheral neuropathy).[96-99] [100] Given availability of other NRTIs and the concern for potential didanosine-induced hepatotoxicity in patients with underlying liver disease (those receiving ribavirin as part of Hepatitis C treatment), the		In vivo, a case series failed to demonstrate increased viral loads with patients on HAART, suggesting that d4T may be used with ribavirin.[92] In a prospective kinetic study, ribavirin 800 mg/daily did not affect the intracellular phosphorylation or plasma kinetics of ZDV, 3TC, or d4T in HCV/HIV-co-infected patients when assessed after 8-12 weeks of co-administration.[93] **Avoid combination if possible. Potential for ↑ mitochondrial**

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	In a pharmacokinetic substudy in patients from the ANRS CO-13 HEPAVIH cohort, ribavirin Cmin was similar in abacavir users and non-users, and there was no evidence that abacavir use affected HCV treatment outcomes including rapid (RVR), early (EVR) and sustained (SVR) virological response.[87] Achieving adequate ribavirin trough levels via weight-based dosing should overcome any potential negligible effect of abacavir,[88, 89] and there is insufficient evidence to recommend	**However, potential for ↑ mitochondrial toxicity (e.g., lactic acidosis) & hematotoxicity.** In a cohort of 50 HIV/HCV subjects on HAART who started pegylated interferon and weight-adjusted ribavirin, 8/20 (40%) on concomitant AZT developed grade 1 or higher anemia, versus 4/30 (13.3%) of those not on AZT, p=0.04.[94] **Therefore, avoid combination whenever possible;[95] otherwise, close monitoring for toxicity is recommended.**		**coadministration of ribavirin and didanosine is now contraindicated**.[4]		**toxicity (i.e. pancreatitis, lactic acidosis).[96-98]**

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	avoiding this combination.[90]					
Rifabutin		32% ↓ AZT AUC. May require higher AZT doses. [101]		Kinetic study showed no significant interaction.[102] However, case report of undetectable rifabutin levels when co-administered with once daily ddI-BT, due to ↑amount of buffer. Separate once daily ddI-BT from rifabutin by at least 2 hrs to avoid interaction.[103]		No significant interaction.[48]
Rifampin		48% ↓ AZT AUC. and 89% ↑ AZT clearance. May require higher AZT doses.[2, 104, 105]	Population pharmacokinetics of 3TC in 16 HIV-positive subjects were similar before and during rifampin-based therapy for tuberculosis. Interaction unlikely to be of clinical significance.[106]			
Rilpivirine				No dose adjustment is required.		

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				However, didanosine should be administered on an empty stomach at least 2 hours before or 4 hours after rilpivirine, which should be administered after a meal.[107]		
Ritonavir		25% ↓ AZT AUC. Dosage adjustment not recommended.[108, 109]		13% ↑ ddI AUC. Space out by 2.5 hours due to potential formulation incompatibilities.[56, 108, 110]		Prospective study in healthy volunteers of d4T 40 mg single dose plus indinavir 800 mg/ritonavir 200 mg resulted in unchanged d4T Cmax, while d4T AUC ↑ 24%; this was not felt to be clinically significant, and no dosage adjustments are recommended.[57]
Saquinavir		No significant interaction.[111]			No significant interaction.[111]	
Stavudine (d4T)		Antagonism. **Avoid combination.**[6, 112]	No significant interaction.[6]	No kinetic interaction.[37] Additive neuropathy.	Additive neuropathy.	

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Tenofovir	See separate table for tenofovir drug interactions.					
Tetracycline				May ↓ tetracycline levels. Give tetracycline 2 hours before or after ddI.[56]		
Tipranavir	Abacavir ↓ 35-44%. Appropriate doses for the combination of ABC and TPV/r have not been established.	The addition of **tipranavir 900, 1200 or 1500 mg TID** to stable AZT 300 mg BID (n=16) resulted in 46% ↓ AZT AUC (p<0.01); investigators concluded this was not clinically significant.[113] Healthy volunteer, randomized, parallel group study (n=60) of either **TPV/r 500 mg/100 mg or TPV/r 750 mg/200 mg** plus AZT 300 mg BID. At steady state, TPV/r caused a 56%–61% ↓ in ZDV Cmax and a 33%–43% ↓ in	The addition of **tipranavir 900, 1200 or 1500 mg TID** to a stable regimen of 3TC 150 mg BID (n=30) resulted in 27% ↓ 3TC AUC (p<0.01); investigators concluded that this was not clinically significant.[113]	The addition of **tipranavir 900, 1200 or 1500 mg TID** to a stable regimen of **ddI tablets** 200 mg BID (n=4) resulted in 46% ↓ ddI AUC (p=0.22). Investigators concluded that this difference was not clinically significant.[113] Healthy volunteer, randomized, parallel group study (n=23) of either **TPV/r 500 mg/100 mg or TPV/r 750 mg/200 mg** plus **ddI EC** 400 mg daily. At steady state, 32% ↑ Cmax and 34%↓ C12h of TPV,		The addition of **tipranavir 900, 1200 or 1500 mg TID** to a stable regimen of d4T 40 mg BID (n=15) resulted in 15% ↓ d4T AUC (p<0.02). Investigators concluded that this difference was not clinically significant.[113]

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		AUC. ZDV did not affect the PK of TPV/r.[114] Appropriate doses for the combination of ZDV and TPV/r have not been established.		although overall TPV AUC unchanged; no change in ddI PK observed. [114] **Suggest giving ddI EC 2 hours apart from TPV/r.**		
Trimethoprim-Sulfamethoxazole		23% ↑ in AZT AUC due to TMP component. May be more pronounced in hepatic failure. Monitor for AZT toxicity.[115]	43% ↑ 3TC AUC. No dosage adjustment required. Monitor for 3TC side-effects (i.e. GI, headache, fatigue, myalgias, ↓ ANC).[116]			
Valganciclovir				Case report of acute pancreatitis with combination. Given significant interaction with ddI and ganciclovir, caution is warranted with this combination.[117]		
Valproic acid		80% ↑ AZT AUC.[118] Use together with caution, and monitor for AZT toxicity; severe anemia has been				

	Abacavir (ABC) Ziagen®[1]	Zidovudine (AZT) Retrovir® [2]	Lamivudine (3TC) 3TC®[3]	Didanosine (ddI) Videx®, Videx EC®[4]	Zalcitabine (ddC) Hivid®[5]	Stavudine (d4T) Zerit®[6]
		reported with combination secondary to increased levels of AZT.[119]				
Zalcitabine (ddC)		No significant interaction.[5]	Antagonism. **Avoid combination.**[64]	Additive toxicities. **Avoid combination**[5, 36]		Additive neuropathy.
Zidovudine (AZT)	24% ↑ AZT AUC. No change in ABC levels.[60]		No significant kinetic interaction.[3] Case reports of profound anemia with combination.[61, 62] 3TC may resensitize AZT to HIV.[63]	19% ↑ ddI AUC; 35% ↓ AZT AUC. No dosage adjustments required. [34]	No significant interaction.[5]	Antagonism. **Avoid combination.**[6, 112]

Please note: This chart summarizes some of the major drug interactions identified to date, based on current available data; other drug interactions may exist. Please use caution whenever adding/modifying therapy. The information in this table is intended for use by experienced physicians and pharmacists. It is not intended to replace sound professional judgment in individual situations, and should be used in conjunction with other reliable sources of information. Due to the rapidly changing nature of information about HIV treatment and therapies, users are advised to recheck the information contained herein with the original source before applying it to patient care.

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