

**PHARMACOKINETIC AND PHARMACODYNAMIC DRUG INTERACTIONS
WITH TENOFOVIR (VIREAD®)**

	Interaction	Dosing Recommendation
Usual Dose	300 mg once daily with food.	
Kinetic Characteristics	Following oral administration, tenofovir is hydrolyzed in the systemic circulation into active parent nucleotide which is almost exclusively renally cleared by a combination of glomerular filtration and active tubular transport.	
Food	Take with food.	
A) PHARMACOKINETIC INTERACTIONS:		
a. NUCLEOSIDE ANALOGUES		
Abacavir	<p>In a pharmacokinetic study of 8 HIV+ individuals, single dose abacavir was administered alone and with tenofovir. The pharmacokinetics of both drugs were unchanged during coadministration compared to historical controls.¹</p> <p>In a separate prospective study of 15 patients on stable tenofovir/abacavir/3rd NRTI, intracellular concentrations of tenofovir DP were not significantly altered in either the presence or absence of abacavir and vice versa. Therefore, an intracellular drug interaction between tenofovir and abacavir does not appear to exist.²</p> <p>In contrast, a non-additive antiviral effect was observed when abacavir and tenofovir were administered for 7 days alone or in combination in 21 HIV-infected, treatment naïve subjects in a randomized trial. In study participants, the viral decay during ABC and TDF dual-therapy was similar to that during ABC therapy alone. This negative pharmacodynamic interaction was not explained by changes in CBV-TP or TFV-DP concentrations. Rather, modest increases in endogenous dATP pools were associated with reduced antiviral potency of TDF during co-administration with ABC.³</p>	<p>No dosage adjustment required. Suboptimal virologic response of QD tenofovir, abacavir and lamivudine may be due to a negative pharmacodynamic effect.</p> <p><i>*see also section (B) for information on pharmacodynamic interactions.</i></p>
Didanosine (ddl)	<p>TDF kinetics are unchanged, however ddl kinetics are significantly altered depending on the ddl formulation used.</p> <p>ddl-tablets (BT):</p> <p>Tenofovir 300 mg daily plus ddl 400 mg 1 hour before in healthy volunteers: 40% ↑ AUC and 28% ↑ Cmax of ddl.⁴</p> <p>ddl-EC:</p> <p>400 mg + TDF:</p> <ul style="list-style-type: none"> • staggered dosing (ddl-EC given fasting, 2 hours before TDF): 48% ↑ Cmax & AUC of ddl-EC • coadministered with light meal: 64% ↑ Cmax, 60% ↑ AUC ddl-EC⁵ <p>ddl-EC 250 mg + TDF:</p> <ul style="list-style-type: none"> • staggered dosing (ddl-EC given fasting, 2 hours before TDF), or simultaneous dosing with/ without a light meal: ddl AUC equivalent to that of 400 mg ddl alone⁶ <p>Mechanism possibly related to phosphorylated tenofovir</p>	<p>Use 250 mg ddl-EC when coadministering with tenofovir 300 mg with food.</p> <p>Monitor for ddl-related toxicities. Discontinue ddl if signs/symptoms of pancreatitis, symptomatic hyperlactatemia, or lactic acidosis develop.</p> <p><i>*see also section (B) for information on pharmacodynamic</i></p>

	Interaction	Dosing Recommendation
	metabolite inhibition of purine nucleoside phosphorylase enzyme (PNP), which is responsible for ddl breakdown. ⁷ A significant intracellular interaction between ddl and tenofovir has not been observed. ^{8,9}	<i>interactions with ddl.</i>

NB: The European Medicines Agency (EMA) issued a statement on March 3, 2005, alerting health care providers to safety and efficacy concerns regarding tenofovir and ddl coadministration. In its statement, the EMA noted that using ddl and tenofovir together was not recommended in any combination of anti-HIV agents, particularly in PHAs with high viral loads (100,000 copies or greater) or low CD4+ cell counts (less than 200 cells). The EMA noted that rare, occasionally fatal, cases of pancreatitis and lactic acidosis have been observed when the drugs have been used together and advised that if using ddl and tenofovir together was "strictly necessary", subjects should be closely monitored for ddl-related side effects as well as regimen efficacy.

[EMA. *Efficacy and safety concerns regarding the co-administration of tenofovir disoproxil fumarate (TDF, Viread) and didanosine (ddl, Videx). Public Statement 3 March, 2005.*
<http://www.emea.eu.int/pdfs/human/press/pus/6233105en.pdf>]

Emtricitabine (FTC)	In healthy volunteers, coadministration of tenofovir 300 mg QD and FTC 200 mg QD for 7 days did not affect steady-state concentrations of either drug. ¹⁰	Combination may be coadministered without dosage adjustment.
Lamivudine (3TC)	In healthy volunteers, tenofovir 300 mg daily plus 3TC 150 mg BID resulted in slightly delayed Tmax and ↓ Cmax of 3TC, but overall 3TC AUC was unchanged; tenofovir kinetics were not altered. ¹¹ In HIV-infected subjects, no interaction was observed between tenofovir and lamivudine at the plasma and intracellular levels. ¹²	Combination may be coadministered without dosage adjustment.
Stavudine (d4T)	Kinetic study in 18 healthy volunteers of tenofovir +/- d4T XR 100 mg showed no differences in kinetics of either drug when coadministered. ¹³	Combination may be coadministered without dosage adjustment.

b. NON-NUCLEOSIDE ANALOGUES

Efavirenz	In healthy volunteers, coadministration of tenofovir 300 mg and efavirenz 600 mg did not affect steady-state concentrations of either drug. ¹¹	Combination may be coadministered without dosage adjustment.
Etravirine (TMC125)	Coadministration of tenofovir 300 mg QD plus etravirine 200 mg BID in healthy volunteers led to 19% ↓ Cmax and AUC and 18% ↓ Cmin of etravirine, while tenofovir Cmax and AUC ↑ 15%. Combination may be coadministered without dosage adjustment. ¹⁴ Tenofovir was associated with 26% ↓ etravirine AUC12h from population PK data from substudy in DUET trials. ¹⁵	Combination may be coadministered without dosage adjustment.
Nevirapine	Trough nevirapine levels (23-25 hours post-dose) were obtained in subjects taking NVP 400 mg QD with or without concomitant tenofovir. The mean NVP concentration was 3420 (range 3170-3670) ng/mL in those taking NVP and tenofovir (n=171) and 3260 (range 2980-3540) ng/mL in those taking NVP without tenofovir (n=87). ¹⁶	Combination may be coadministered without dosage adjustment.
Rilpivirine	In healthy volunteers, coadministration of rilpivirine 150 mg QD and tenofovir 300 mg QD for 8 days resulted in 24% ↑	No dosage adjustments of either

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(TMC278)	AUC, 21% ↑ Cmax and 24% ↑ Cmin of tenofovir, while kinetics of rilpivirine were not affected. ¹⁷	drug recommended.
c. PROTEASE INHIBITORS		
Atazanavir	<p>Combination of atazanavir and tenofovir (at standard doses) resulted in 25% ↓ AUC and 40% ↓ Cmin of atazanavir, while tenofovir AUC was ↑ by 24%; avoid concomitant use.¹⁸</p> <p>In a separate randomized multi-dose interaction study in healthy volunteers, 2 dosing strategies involving unboosted ATV and tenofovir were studied:¹⁹</p> <p>a) ATV 400 mg QD am plus tenofovir 300 mg QD pm:</p> <ul style="list-style-type: none"> • ↓ Cmax 10%, ↓ AUC 17%, ↓ Cmin 28% of ATV • ↑ Cmax 43%, ↑ AUC 37%, ↑ Cmin 38% of TDF <p>b) ATV 600 mg plus tenofovir 300 mg both Qam:</p> <ul style="list-style-type: none"> • ↑ Cmax 27%, ↑ AUC 36%, ↑ Cmin 41% of ATV • ↑ Cmax 41%, ↑ AUC 59%, ↑ Cmin 74% of TDF 	Use atazanavir 300 mg/ ritonavir 100 mg QD plus tenofovir (results in higher Cmin of atazanavir vs. atazanavir 400 mg alone).
Atazanavir/ ritonavir	<p>In a pharmacokinetic substudy (n=10) of HIV+ subjects participating in the Puzzle2-ANRS 107 study, the pharmacokinetics of atazanavir 300/ritonavir 100 mg QD were assessed before and after the addition of tenofovir and other optimized NRTIs. After the addition of tenofovir, atazanavir AUC ↓ 25% (p=0.05) and Cmin ↓ 23% (p=n.s.); tenofovir exposure was not assessed.²⁰</p> <p>In an open-label study of healthy volunteers, temporal separation of tenofovir and atazanavir 300/ritonavir 100 mg 11% ↓ AUC, 20% ↓ Cmin of atazanavir, and 37% ↑ AUC and 29% ↑ Cmin of tenofovir. Simultaneous administration of tenofovir and atazanavir 400/100 mg led to 38% ↑ AUC and 33% ↑ Cmin of atazanavir compared to 300/100 mg alone, but tenofovir AUC ↑ 55% and Cmin ↑ 70%; thus, this dosage combination is not recommended.²¹</p>	<p>Clinical significance unclear. Dosing tenofovir separately from atazanavir/rtv does not offer any clinical advantages over simultaneous administration.</p> <p>Monitor for atazanavir efficacy and tenofovir toxicity.</p>
Breacanavir (GW640385)/ ritonavir	In a randomized, open-label crossover study in healthy volunteers, the combination of breacanavir 300 mg/ritonavir 100 mg BID plus tenofovir 300 mg daily resulted in increased tenofovir exposure (24% ↑ Cmax, 32% ↑ AUC) and modest increases in breacanavir exposure (14% ↑ AUC, 17% ↑ Cmax, 20% ↑ Cmin). ²²	Combination may be coadministered without dosage adjustment. Monitor for potential tenofovir toxicity.
Darunavir (TMC114)/ ritonavir	Multidose study of tenofovir 300 mg QD plus darunavir (oral solution) 300 mg/ritonavir 100 mg BID led to 22% ↑ tenofovir exposure (statistically significant), while darunavir kinetics were not significantly affected.	Combination may be used without dose adjustments.
Fosamprenavir/ ritonavir	In healthy volunteers, tenofovir 300 mg daily plus fosamprenavir 1400/ritonavir 100 mg QD or fosamprenavir 1400/ritonavir 200 mg QD for 14 days showed no change in amprenavir AUC and a non-significant increase in Cmin. A non-significant increase in ritonavir AUC and Cmax were observed in the FPV 1400/rtv 200 mg arm in the presence of	Combination may be coadministered without dosage adjustment.

	Interaction	Dosing Recommendation
	<p>tenofovir.²³</p> <p>Similarly, in an open-label study of 15 treatment-naïve subjects, FPV 1400/rtv 200/tenofovir 300/emtricitabine 200 mg QD for 48 weeks yielded antiretroviral concentrations similar to historical controls.²⁴</p> <p>In a cohort of 21 HIV-infected subjects taking fosamprenavir 700/ritonavir 100 mg BID plus tenofovir and an NRTI, steady-state C_{min} concentrations of amprenavir, ritonavir and tenofovir were within the therapeutic range and comparable to historical controls.²⁵</p> <p>In a healthy volunteer study, subjects received tenofovir 300 mg QD for 7 days (period 1), and then were randomized to receive fosamprenavir 1400 mg BID or fosamprenavir 700/rtv 100 mg BID alone and with tenofovir or vice versa (periods 2 & 3). Tenofovir C_{min}, C_{max} and AUC ↓ 12%, 25% and 15% with fosamprenavir and ↓ 9%, 18% and 7% with boosted fosamprenavir, respectively. In the presence of tenofovir, amprenavir C_{min}, C_{max} and AUC ↑ 31%, 3% and 7% (unboosted) and ↑ 31%, 4% and 16% (boosted). These changes are not likely clinically significant.²⁶</p>	
Indinavir (IDV)	In healthy volunteers, tenofovir 300 mg daily plus indinavir 800 mg q8h resulted in slightly delayed T _{max} and ↓ C _{max} of indinavir, but overall AUC was unchanged; tenofovir C _{max} was slightly ↑ but AUC unchanged. These changes not likely to be clinically significant. ¹¹	Combination may be coadministered without dosage adjustment.
Lopinavir/ritonavir	<p><i>Impact on tenofovir:</i></p> <ul style="list-style-type: none"> In healthy volunteers, tenofovir 300 mg daily plus lopinavir 400/ritonavir 100 mg BID resulted in slight ↑ AUC, C_{max} of tenofovir; lopinavir AUC and C_{max} were ↓ 15%, but C_{min} unchanged and lopinavir IQ-wild type >90. These changes not likely clinically significant.¹¹ In a crossover study in healthy volunteers, TDF plus LPV/r with food led to ↑ 32% tenofovir AUC, while LPV and RTV kinetics were not affected. Clinical significance unclear.²⁷ In tenofovir compassionate access study, (median duration of 63 weeks), 94% of patients received TDF + LPV/r (n = 274/291), with no significant nephrotoxicity observed.²⁸ In a small cross-sectional study of HIV-positive subjects on tenofovir with lopinavir/ritonavir or nevirapine, tenofovir C_{max} ↑ 39% and AUC ↑ 72% in the presence of lopinavir/ritonavir versus nevirapine. Intracellular tenofovir-diphosphate AUC was also ↑ 35% in the presence of lopinavir/ritonavir compared to nevirapine.¹² 	<p>Recommendations on dosage adjustment not established.</p> <p>Monitor for tenofovir toxicity and possibly lopinavir efficacy, particularly in treatment-experienced patients. Consider TDM (if available) with possible dosage increase of lopinavir if suboptimal lopinavir concentrations and/or inadequate viral response.³¹</p>

	Interaction	Dosing Recommendation
	<p><i>Impact on lopinavir/ritonavir concentrations:</i></p> <ul style="list-style-type: none"> Retrospective data from a series of HIV subjects (n=10) showed no effect of tenofovir on lopinavir and ritonavir C_{min} at steady-state.²⁹ In patients taking LPV/r and TDF (n=14), mean lopinavir C_{trough} was 5.6 ug/mL vs. 7 ug/mL in patients taking LPV/r plus other NRTIs (n=15).³⁰ In a pharmacokinetic interaction study in experienced patients (n=18), lopinavir C_{min} ↓ by 34% (mean 4.61 vs. 3.06 ug/mL, p=0.04), while ritonavir C_{min} ↓ by 44% (mean of 0.63 vs. 0.35 ug/mL, p=0.014) in the presence of tenofovir.³¹ 	
Nelfinavir	<p>In 18 patients stabilized on nelfinavir 1250 mg BID, addition of tenofovir 300 mg QD for 7 days did not affect the AUC of nelfinavir.³²</p> <p>A separate pharmacokinetic study in 29 healthy volunteers showed no significant changes in the kinetics of nelfinavir/M8 or tenofovir when coadministered at usual doses.³³</p>	Combination may be coadministered without dosage adjustment.
Ritonavir	<p>An in vitro study using renal epithelial cell lines overexpressing MRP2 showed that tenofovir alone was not nephrotoxic, even at high doses. However, when tenofovir was combined with MRP2 inhibitors such as LPV, RTV, cyclosporine or MK571, TDF efflux was reduced and intracellular TDF concentrations increased, with cellular toxicity observed at high concentrations.³⁴</p> <p>In a retrospective database analysis, tenofovir subjects receiving ritonavir-boosted regimens appeared to be predisposed to developing renal insufficiency.³⁵</p>	<p>Recommendations on dosage adjustment not established.</p> <p>Monitor for tenofovir toxicity.</p>
Saquinavir	<p>In cohort (n=14) of patients on saquinavir-hgc 1600 mg/ritonavir 100 mg QD, no significant difference in saquinavir C_{min} when NRTI backbone switched from ddl/d4T to tenofovir/3TC.³⁶</p> <p>Separate study of saquinavir-hgc 1000 mg/ritonavir 100 mg BID and tenofovir (n=18 HIV+ adults) showed no change in tenofovir PK parameters with coadministration.³⁷ Similar effect observed in healthy volunteer study.³⁸</p>	Combination may be coadministered without dosage adjustment.
Telaprevir (investigational HCV protease inhibitor), substrate and inhibitor of CYP3A4 and pgg	<p>In an open-label, randomized 3-way crossover study, healthy volunteers received tenofovir 300 mg QD, telaprevir 750 mg q8h or the combination, each for 7 days. All doses were administered with food. Tenofovir C_{min} ↑ 41%, C_{max} ↑ 30% and AUC ↑ 30% in the presence of telaprevir, while telaprevir kinetics were unchanged by tenofovir.³⁹</p>	
Tipranavir	<p>Healthy volunteer, randomized, parallel group study (n=49) of either TPV/r 500 mg/100 mg or TPV/r 750 mg/200 mg plus tenofovir 300 mg daily. At steady state, a dose-dependent ↓</p>	May consider using TPV/r plus tenofovir without further dosage

	Interaction	Dosing Recommendation
	in TDF Cmax of 23%–38% was shown, and 17% and 11% ↓ in TPV at the 500/100 and 750/200 doses, respectively. ⁴⁰	adjustment.
d. CCR5 ANTAGONISTS		
Aplaviroc	Healthy volunteer, randomized study of tenofovir 300 mg daily and aplaviroc 600 mg BID showed no significant effect of tenofovir on aplaviroc AUC or Cmax, and a moderate increase in Cr of 80%. Tenofovir pharmacokinetics were not changed in the presence of aplaviroc. ⁴¹	Combination may be coadministered without dosage adjustment.
Maraviroc	Healthy volunteer, randomized, placebo-controlled crossover trial in 11 healthy subjects of maraviroc 300 mg BID + tenofovir 300 mg QD/placebo for 7 days showed no significant changes in maraviroc AUC and Cmax in the presence of tenofovir. ⁴²	Combination may be coadministered without dosage adjustment.
Vicriviroc	Healthy volunteer, randomized study of vicriviroc 10 mg BID +/- tenofovir 300 mg QD for 7 days showed no significant changes in vicriviroc Cmax, AUC, clearance or terminal t1/2 in the presence of tenofovir. ⁴³	Combination may be coadministered without dosage adjustment.
e. INTEGRASE INHIBITORS		
Dolutegravir (S/GSK134957 2)	No clinically relevant drug interaction observed when healthy subjects received dolutegravir 50 mg QD and tenofovir 300 mg QD for 5 days compared to either drug administered alone. Dolutegravir and tenofovir can be coadministered without dose adjustment. ⁴⁴	Combination may be coadministered without dosage adjustment.
Elvitegravir (GS-9137)	No clinically relevant drug interaction observed when healthy subjects (n=24) received GS-9137 50 mg/rtv 100 mg QD with or without emtricitabine 200 mg/tenofovir 300 mg QD. ⁴⁵	Combination may be coadministered without dosage adjustment.
Raltegravir (MK-0518)	In an open-label, 3-period study in 10 healthy subjects, combination of 400 mg MK-0518 BID and 300 mg QD of tenofovir for 4 days led to modest increases in MK-0518 AUC (49%) and Cmax (64%) while Cmin was unchanged; tenofovir AUC ↓ 10% and Cmin ↓ 13%. ⁴⁶	Dose adjustment likely not necessary.
f. OTHER MEDICATIONS		
Adefovir	The single dose kinetics of adefovir were studied alone and in the presence of multi-dose tenofovir in 22 subjects. The pharmacokinetic parameters of both adefovir and tenofovir (including renal clearance) ⁴⁷ were unchanged when both drugs were given together.	Dose adjustment not necessary.
Buprenorphine	In 27 opioid-dependent, buprenorphine/naloxone-maintained, HIV-negative volunteers, no significant changes in buprenorphine pharmacokinetics were observed following ddl, 3TC and tenofovir administration, and buprenorphine had no statistically significant effect on NRTI concentrations. ⁴⁸	Dose adjustment not necessary.
Methadone (oral)	Methadone pharmacokinetics and dynamics not affected by tenofovir. Combination appears safe. ⁴⁹	Dose adjustment likely not necessary.

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Oral Contraceptives	In an open-label, 29 day study in healthy volunteers, coadministration of tenofovir 300 mg and oral contraceptives did not affect steady-state concentrations of tenofovir or either the estrogenic or progestational components of oral contraceptives. ⁵⁰	Combination may be coadministered without dosage adjustment.
Ribavirin	Kinetic study in 22 healthy subjects of single 600 mg dose ribavirin and multi-dose tenofovir showed no significant changes in ribavirin PK. ⁵¹	Dose adjustment likely not necessary.
Rifampin	Steady-state interaction study in healthy subjects of tenofovir and rifampin 600 mg daily did not show clinically significant changes in PK of either drug. ⁵²	Combination may be coadministered without dosage adjustment.
B) PHARMACODYNAMIC INTERACTIONS:		
a. ANTIRETROVIRAL COMBINATIONS TO AVOID BECAUSE OF DECREASED VIRAL EFFICACY		
1) Initiation Studies in Naïve Subjects		
Tenofovir, lamivudine, didanosine	In a small pilot study (n=22) of treatment-naïve subjects started on didanosine + tenofovir + lamivudine, a high rate (91%) of virologic failure (defined as <2 log reduction of HIV-RNA by week 12) was seen observed. ⁵³	3-NRTI regimen of TDF/3TC/ddI should not be used in any patient. ⁵³
Tenofovir, lamivudine, abacavir	In an interim analysis of treatment naïve patients randomized to receive abacavir/lamivudine plus tenofovir or efavirenz (n=194 with 8 week data), those randomized to abacavir/tenofovir/lamivudine had a significantly higher rate of early virologic non-response (defined as <2 log drop in viral load by week 8 or 1 log rebound from nadir) compared to patients treated with efavirenz/abacavir/lamivudine (49% vs. 5%, p<0.001). ⁵⁴	3-NRTI regimen of TDF/3TC/ abacavir should not be used in any patient. ⁵⁴
Tenofovir, didanosine, efavirenz	A randomized, open-label study of ddl/efavirenz plus tenofovir (n=41) or lamivudine (N=36) in 77 naïve patients was terminated prematurely, following an unplanned interim analysis. At week 4 (ITT), the tenofovir and lamivudine groups had similar viral loads, but by week 12, the tenofovir group had a significantly higher VL compared to the 3TC group (2.28 log copies/mL vs. 1.83, p=0.013), and there were 5 failures with emergent RT mutations in the TDF arm vs. 0 in the 3TC arm, p<0.05. All failures had VL>100,000 and CD4<200, with >99% adherence, and 3 subjects showed low efavirenz levels. ⁵⁵ An open-label, randomized pilot study comparing tenofovir/ddI-EC 250 mg/efavirenz +/- lopinavir/ritonavir in naïve subjects was terminated prematurely, following an unplanned interim analysis. At 3 months follow-up in 29 patients, 7/15 (46.7%) of the 3-ARV arm developed early virologic failure by ITT (5 had virologic failure defined as drop of <2 log at month 3 or rebound >1 log from nadir, 1 lost, 1 switch), compared to 2/14 in the LPV/r arm (1 lost, 1 switch), P=0.109. In the 3-ARV arm, all 6 subjects who experienced virologic failure had baseline VL>100,000 and CD4<200.	Until further information are available, avoid tenofovir/ddI/ efavirenz regimen in patients with VL>100,000 and CD4<200.

	Interaction	Dosing Recommendation
	<p>The following resistance mutations were detected at failure: G190S/E +/- K103N (n=5), K103N/L100I/V108I (n=1), L74V/I (n=4) and K65R (n=2).⁵⁶</p> <p>In a prospective, single-arm study of tenofovir, ddl-EC 250 mg and efavirenz in naïve-subjects, an unplanned interim analysis of 35 subjects who reached week 12 showed a 28% (n=11) virological failure rate (ITT). Of these, 8 subjects failed to achieve VL<400 by week 12, and 3 rebounded to VL>400 between weeks 12 and 24. Six of 11 patients with virologic failure had initial viral load > 100,000 copies/mL and CD4+ count < 200 cells/mm³.⁵⁷</p> <p>A prospective, randomized pilot in naïve subjects compared AZT/3TC/lopinavir-ritonavir (n=8), tenofovir/3TC/efavirenz (n=10) and tenofovir/ddl/efavirenz (n=10). By week 28, 87.5% of the AZT/3TC arm vs. 100% of TDF/3TC arm vs. 60% of the TDF/ddl arm reached undetectable RNA. The HIV-RNA slope was significantly slower in the TDF/ddl arm vs. TDF/3TC arm at days 1, 3, 7, 14 and 28, p<0.0001. Efavirenz AUC values were lower in the TDF/ddl arm compared to the TDF/3TC arm, especially in subjects with early virologic failure.⁵⁸</p>	
Tenofovir, didanosine EC, efavirenz or nevirapine	In a retrospective database analysis of 5000 naïve subjects initiated on HAART between October 2002-March 2004, 14 patients received tenofovir, ddl EC and either efavirenz (n=10) or nevirapine (n=4) once daily. After 12 weeks of treatment, 5/14 (36%) of these patients experienced suboptimal virologic responses (viral load drop <2 log), and 2 additional patients who responded at week 12 experienced virologic rebound (>200 copies/mL on 2 separate occasions) by week 24. Overall, the 7/14 (50%) patients with viral failure (2/4 on NVP, 5/10 on EFV), had a median baseline VL of 5.8 (4.7-6) and CD4 126 (24-281). Resistance mutations at failure: K65R and L74V (n=4), one or more of L100I, K103N/R/T, Y181C, G190E/Q/S (n=7). ⁵⁹	Until further information are available, use caution when coadministering tenofovir/ddl EC and efavirenz or nevirapine in treatment-naïve patients with high baseline viral loads.
Tenofovir, 3TC and nevirapine	In a prospective, randomized, open-label clinical trial of tenofovir, 3TC and nevirapine QD vs. AZT/3TC and nevirapine BID in 71 antiretroviral naïve subjects, 9/36 (25%) virologic failures (<2 log drop or rebound >1 log after initial decline) were noted in the QD, 8 of which occurred by week 12, as compared to 1/35 virologic failure (3%) after week 12 in the BID arm. Those with virologic failure had significantly lower baseline CD4 cell counts (110 vs. 223 cells/mm ³) and higher baseline viral loads (262,747 vs. 51,189 copies/mL) than those with virologic success (p=.004 and .002, respectively); nevirapine trough concentrations were not correlated with risk of failure. A high incidence of NNRTI resistance mutations were seen among the virologic failures (K65R mutation in 6/9, Y181C/A in 7/9, two or more mutations in 5/9). The reasons for the failures are unclear. ⁶⁰	Until further information are available, may wish to avoid using the combination of tenofovir, 3TC and nevirapine in treatment-naïve patients, particularly those with high baseline viral loads and low CD4 counts.

	Interaction	Dosing Recommendation
	Similar results were observed in an open-label trial of 23 antiretroviral naïve subjects prescribed the same QD regimen. In this group, only 10/23 (43%) achieved viral success (VL<75 copies/mL) at 24 weeks ITT; among patients who failed, 7 had virologic failure (6 within the first 8 weeks of treatment), 3 developed rash and 3 were lost to followup. Genotypic analysis of the 7 virologic failures showed Y181C mutation in 5/7 patients, M184V in 3/7 patients, and K65R in 1/7 patients. All 7 virologic failures reported 100% adherence rates. ⁶¹	
	2) Switch Studies in Suppressed Subjects	
Tenofovir plus 2 NRTIs	In a review, 55 patients previously suppressed on a stable regimen (VL<50 for 24 months) were switched to tenofovir plus 2 NRTIs, primarily for toxicity or intolerance (74%); 65.5% had previously broken through on a 3TC-containing regimen or had received suboptimal NRTI therapy. After 24 weeks, only 17 (31%) remained suppressed; 26 (47%) had VL>50 copies/mL, 10 (18%) stopped due to toxicity, and 2 (4%) were lost to follow-up. When compared with other regimens, a regimen that included ddl had a significantly poorer virological success rate (1/21 (5%) vs. 16/34 (47.1%), p=0.001), whereas those that included AZT did relatively better (3/4 (75%) remained suppressed versus 14/51 (27%), p=0.083). In multivariate analysis, use of ddl + tenofovir was significantly associated with a higher probability of failure (OR=17.7, p=0.007). Genotype testing on 8 subjects at failure revealed K65R (n=4) plus either M184V or TAM. ⁶²	Simplification strategy to a tenofovir-2 NRTI regimen (particularly those containing ddl) should used with caution, especially in those with previous RT mutations.
Abacavir, 3TC, tenofovir	In a retrospective database review, 8 subjects previously suppressed on a stable regimen (VL<50 for median 14.2 months) were switched to abacavir-3TC-tenofovir for simplification or toxicity reasons. Five of 8 subjects had viral rebound after a median 130 days (54-160). Four of the 5 subjects had either K65R, M184V/I or both at failure. ⁶³	Simplification strategy to abacavir-3TC-tenofovir should used with caution, especially in those with previous RT mutations.
b. INCREASED TOXICITY		
Didanosine	Paradoxical ↓ in CD4 counts in patients virally suppressed on combination. ^{64, 65} Using 250 mg ddl with TDF may lead to partial improvement in CD4 counts. ⁶⁶	Reduce didanosine dose to 250 mg QD when administering with tenofovir. Monitor response, including CD4 counts, particularly after 6 months of therapy.
	Case reports of pancreatitis ^{67, 68} , fatal lactic acidosis ^{69, 70} , and/or renal failure ⁷¹ reported with combination of didanosine and tenofovir.	Monitor for toxicity.

	Interaction	Dosing Recommendation
<p>NB: The European Medicines Agency (EMA) issued a statement on March 3, 2005, alerting health care providers to safety and efficacy concerns regarding tenofovir and ddl coadministration. In its statement, the EMA noted that using ddl and tenofovir together was not recommended in any combination of anti-HIV agents, particularly in PHAs with high viral loads (100,000 copies or greater) or low CD4+ cell counts (less than 200 cells). The EMA noted that rare, occasionally fatal, cases of pancreatitis and lactic acidosis have been observed when the drugs have been used together and advised that if using ddl and tenofovir together was "strictly necessary", subjects should be closely monitored for ddl-related side effects as well as regimen efficacy.</p> <p><i>[EMA. Efficacy and safety concerns regarding the co-administration of tenofovir disoproxil fumarate (TDF, Viread) and didanosine (ddl, Videx). Public Statement 3 March, 2005. http://www.emea.eu.int/pdfs/human/press/pus/6233105en.pdf]</i></p>		

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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