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

<table>
<thead>
<tr>
<th>Interaction</th>
<th>Dosing Recommendation</th>
</tr>
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<tbody>
<tr>
<td>Usual Dose</td>
<td>300 mg once daily with food.</td>
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<tr>
<td>Kinetic Characteristics</td>
<td>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.</td>
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<tr>
<td>Food</td>
<td>Take with food.</td>
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</tbody>
</table>

#### A) PHARMACOKINETIC INTERACTIONS:

**a. NUCLEOSIDE ANALOGUES**

**Abacavir**

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. 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.

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. 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.

No dosage adjustment required. Suboptimal virologic response of QD tenofovir, abacavir and lamivudine may be due to a negative pharmacodynamic effect.

*see also section (B) for information on pharmacodynamic interactions.

**Didanosine (ddl)**

TDF kinetics are unchanged, however ddl kinetics are significantly altered depending on the ddl formulation used.

**ddl-tablets (BT):**

Tenofovir 300 mg daily plus ddl 400 mg 1 hour before in healthy volunteers: 40% ↑ AUC and 28% ↑ Cmax of ddl.

**ddl-EC:**

400 mg + TDF:

- 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-EC 250 mg + TDF:**

- 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 alone

Use 250 mg ddl-EC when coadministering with tenofovir 300 mg with food. Monitor for ddl-related toxicities. Discontinue ddl if signs/symptoms of pancreatitis, symptomatic hyperlactatemia, or lactic acidosis develop.

*see also section (B) for information on pharmacodynamic interactions.
**Interaction**

| 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.  
| 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.  
In HIV-infected subjects, no interaction was observed between tenofovir and lamivudine at the plasma and intracellular levels.  
| Stavudine (d4T) | Kinetic study in 18 healthy volunteers of tenofovir +/- d4T XR 100 mg showed no differences in kinetics of either drug when coadministered.  

**Dosing Recommendation**

| Emtricitabine (FTC) | Combination may be coadministered without dosage adjustment.  
| Lamivudine (3TC) | Combination may be coadministered without dosage adjustment.  
| Stavudine (d4T) | 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.  
| Etravirine | 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.  
Tenofovir was associated with 26% ↓ etravirine AUC12h from population PK data from substudy in DUET trials.  
| 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).  
| Rilpivirine | In healthy volunteers, coadministration of rilpivirine 150 mg QD and tenofovir 300 mg QD for 8 days resulted in 24% ↑  

**NB:** The European Medicines Agency (EMEA) issued a statement on March 3, 2005, alerting health care providers to safety and efficacy concerns regarding tenofovir and ddI coadministration. In its statement, the EMEA noted that using ddI 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 EMEA 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 ddI and tenofovir together was “strictly necessary”, subjects should be closely monitored for ddI-related side effects as well as regimen efficacy.  
[EMEA. Efficacy and safety concerns regarding the co-administration of tenofovir disoproxil fumarate (TDF, Viread) and didanosine (ddI, Videx). Public Statement 3 March, 2005.  
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<td>AUC, 21% ↑ Cmax and 24% ↑ Cmin of tenofovir, while kinetics of rilpivirine were not affected.(^{17})</td>
<td>drug recommended.</td>
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</table>

c. PROTEASE INHIBITORS

**Atazanavir**
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.\(^{18}\)
In a separate randomized multi-dose interaction study in healthy volunteers, 2 dosing strategies involving unboosted ATV and tenofovir were studied:\(^{19}\)

a) ATV 400 mg QD am plus tenofovir 300 mg QD pm:
   - ↓ Cmax 10%, ↓ AUC 17%, ↓ Cmin 28% of ATV
   - ↑ Cmax 43%, ↑ AUC 37%, ↑ Cmin 38% of TDF

b) ATV 600 mg plus tenofovir 300 mg both Qam:
   - ↑ 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**
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.\(^{20}\)
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.\(^{21}\)
Clinical significance unclear. Dosing tenofovir separately from atazanavir/rtv does not offer any clinical advantages over simultaneous administration. Monitor for atazanavir efficacy and tenofovir toxicity.

**Brecanavir (GW640385)/ritonavir**
In a randomized, open-label crossover study in healthy volunteers, the combination of brecanavir 300 mg/ritonavir 100 mg BID plus tenofovir 300 mg daily resulted in increased tenofovir exposure (24% ↑ Cmax, 32% ↑ AUC) and modest increases in brecanavir 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 ampranavir 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
**Interaction**

**Recommendation**

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<td>Combination may be coadministered without dosage adjustment.</td>
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<tr>
<td>Lopinavir/ritonavir</td>
<td>Recommendations on dosage adjustment not established. <strong>Monitor for tenofovir toxicity and possibly lopinavir efficacy,</strong> particularly in treatment-experienced patients. Consider TDM (if available) with possible dosage increase of lopinavir if suboptimal lopinavir concentrations and/or inadequate viral response.</td>
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**Impact on tenofovir:**

- In healthy volunteers, tenofovir 300 mg daily plus lopinavir 400/ritonavir 100 mg BID resulted in slight ↑ AUC, Cmax of tenofovir; lopinavir AUC and Cmax were ↓ 15%, but Cmin unchanged and lopinavir IQ-wild type >90. These changes not likely clinically significant.  
- 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.  
- 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.  
- In a small cross-sectional study of HIV-positive subjects on tenofovir with lopinavir/ritonavir or nevirapine, tenofovir Cmax ↑ 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.  

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23 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 In a cohort of 21 HIV-infected subjects taking fosamprenavir 700/ritonavir 100 mg BID plus tenofovir and an NRTI, steady-state Cmin concentrations of amprenavir, ritonavir and tenofovir were within the therapeutic range and comparable to historical controls.  

25 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 Cmin, Cmax and AUC ↓ 12%, 25% and 15% with fosamprenavir and ↓ 9%, 18% and 7% with boosted fosamprenavir, respectively. In the presence of tenofovir, amprenavir Cmin, Cmax and AUC ↑ 31%, 3% and 7% (unboosted) and ↑ 31%, 4% and 16% (boosted). These changes are not likely clinically significant.  

26 Indinavir (IDV) In healthy volunteers, tenofovir 300 mg daily plus indinavir 800 mg q8h resulted in slightly delayed Tmax and ↓ Cmax of indinavir, but overall AUC was unchanged; tenofovir Cmax was slightly ↑ but AUC unchanged. These changes not likely to be clinically significant.  

27 Lopinavir/ritonavir

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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.  

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31 Recommendations on dosage adjustment not established. **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.
### Interaction Dosing Recommendation

**Impact on lopinavir/ritonavir concentrations:**

- Retrospective data from a series of HIV subjects (n=10) showed no effect of tenofovir on lopinavir and ritonavir Cmin at steady-state.\(^2^9\)
- In patients taking LPV/r and TDF (n=14), mean lopinavir Ctrough was 5.6 ug/mL vs. 7 ug/mL in patients taking LPV/r plus other NRTIs (n=15).\(^3^0\)
- In a pharmacokinetic interaction study in experienced patients (n=18), lopinavir Cmin ↓ by 34% (mean 4.61 vs. 3.06 ug/mL, p=0.04), while ritonavir Cmin ↓ by 44% (mean of 0.63 vs. 0.35 ug/mL, p=0.014) in the presence of tenofovir.\(^3^1\)

**Nelfinavir**

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.\(^3^2\) 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.\(^3^3\)

**Ritonavir**

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.\(^3^4\)

In a retrospective database analysis, tenofovir subjects receiving ritonavir-boosted regimens appeared to be predisposed to developing renal insufficiency.\(^3^5\)

**Saquinavir**

In cohort (n=14) of patients on saquinavir-hgc 1600 mg/ritonavir 100 mg QD, no significant difference in saquinavir Cmin when NRTI backbone switched from ddI/d4T to tenofovir/3TC.\(^3^6\)

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.\(^3^7\) Similar effect observed in healthy volunteer study.\(^3^8\)

**Tipranavir**

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 ↓ in TDF Cmax of 23%–38% was shown, and 17% and 11% ↓ in TPV at the 500/100 and 750/200 doses, respectively.\(^3^9\)

May consider using TPV/r plus tenofovir without further dosage adjustment.

### 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 Ct of 80%. Tenofovir pharmacokinetics were not

Combination may be coadministered without dosage adjustment.

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#### 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.  

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.

Combination may be coadministered without dosage adjustment.

### e. INTEGRASE INHIBITORS

#### Dolutegravir (S/GSK1349572)

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.

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.

Combination may be coadministered without dosage adjustment.

#### Raltegravir

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%.

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) were unchanged when both drugs were given together.

Dose adjustment not necessary.

#### Boceprevir

In healthy subjects, there were no clinically relevant changes in boceprevir exposure when co-administered with tenofovir. Boceprevir also had no notable effect on tenofovir AUC or renal clearance, but increased tenofovir Cmax by 32%.

Combination may be coadministered without dosage adjustment.

#### 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.

Dose adjustment not necessary.

#### Cobicistat

In healthy subjects who received cobicistat 150 mg QD or tenofovir 300 mg QD each alone or in combination for seven days, tenofovir Cmax ↑ 42% and AUC ↑ 11% when coadministered with cobicistat. Effect consistent with inhibition of intestinal P-gp-mediated efflux of tenofovir by cobicistat. Tenofovir half-life was unaffected. An in vitro
### Interaction Dosing Recommendation

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<td>Methadone (oral)</td>
<td>Methadone pharmacokinetics and dynamics not affected by tenofovir. Combination appears safe. Dose adjustment likely not necessary.</td>
</tr>
<tr>
<td>Oral Contraceptives</td>
<td>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. Combination may be coadministered without dosage adjustment.</td>
</tr>
<tr>
<td>Ribavirin</td>
<td>Kinetic study in 22 healthy subjects of single 600 mg dose ribavirin and multi-dose tenofovir showed no significant changes in ribavirin PK. Dose adjustment likely not necessary.</td>
</tr>
<tr>
<td>Rifampin</td>
<td>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. Combination may be coadministered without dosage adjustment.</td>
</tr>
<tr>
<td>Telaprevir</td>
<td>In a randomized, open-label study, healthy volunteers received tenofovir 300 mg daily, telaprevir 750 mg q8h, or both drugs, each for 7 days. In the presence of telaprevir, tenofovir AUC$_{24h}$ was increased by 30% while telaprevir kinetics were not affected. In an open-label study, 20 HIV/HCV-negative volunteers started telaprevir 750 mg every 8 hours for 7 days followed by EFV/tenofovir disoproxil fumarate (TDF) 600/300 mg once daily for 7 days after a washout. Subsequently, volunteers received telaprevir 1125 mg every 8 hours and EFV/TDF 600/300 mg once daily for 7 days or telaprevir 1500 mg every 12 hours and EFV/TDF 600/300 mg once daily for 7 days in a randomized order without a washout. Telaprevir was taken with food and EFV/TDF was taken on an empty stomach in the morning. With TVR 1125 mg q8h plus efavirenz/TDF/FTC, telaprevir AUC ↓ 18%, Cmin ↓ 25%, EFV AUC ↓ 18%, Cmin ↓ 10%, and tenofovir AUC ↑ 10% and Cmin ↑ 17%. With TVR 1500 mg q8h plus EFV/TDF/FTC, telaprevir AUC ↓ 20%, Cmin ↓ 48%, EFV AUC ↓ 15%, Cmin ↓ 11%, and tenofovir AUC ↑ 10% and Cmin ↑ 6%. Combination may be coadministered without dosage adjustment.</td>
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### B) PHARMACODYNAMIC INTERACTIONS:

**a. ANTIRETROVIRAL COMBINATIONS TO AVOID BECAUSE OF DECREASED VIRAL EFFICACY**

1) **Initiation Studies in Naïve Subjects**

| 3-NRTI regimen of TDF/3TC/ddI should not be used in any patient.  
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. |

| 3-NRTI regimen of TDF/3TC/abacavir should not be used | 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 |

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October 22, 2013  www.hivclinic.ca
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<td>abacavir/tenofovir/lamivudine had a significantly higher rate of early virologic non-response (defined as &lt;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&lt;0.001).</td>
<td>in any patient.98</td>
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**Tenofovir, didanosine, efavirenz**

A randomized, open-label study of ddI/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.98

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. 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).60

In a prospective, single-arm study of tenofovir, ddI-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/mm³.61

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.62

**Tenoforv, didanosine EC.**

In a retrospective database analysis of 5000 naïve subjects initiated on HAART between October 2002-March 2004, 14

**Until further information are available, avoid tenofovir/ddl/efavirenz regimen in patients with VL>100,000 and CD4<200.**
### Interaction

<table>
<thead>
<tr>
<th>Compound</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>efavirenz or nevirapine</td>
<td>Patients received tenofovir, ddI 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 &lt;2 log), and 2 additional patients who responded at week 12 experienced virologic rebound (&gt;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).</td>
</tr>
<tr>
<td>Tenofovir, 3TC and nevirapine</td>
<td>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 (&lt;2 log drop or rebound &gt;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/mm³) 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.</td>
</tr>
</tbody>
</table>

### Dosing Recommendation

- **efavirenz or nevirapine**: Available, use caution when coadministering tenofovir/ddI EC and efavirenz or nevirapine in treatment-naïve patients with high baseline viral loads.
- **Tenofovir, 3TC and nevirapine**: 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.

### 2) Switch Studies in Suppressed Subjects

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tenofovir plus 2 NRTIs</td>
<td>In a review, 55 patients previously suppressed on a stable regimen (VL&lt;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&gt;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 ddI 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 ddI + tenofovir was Simplification strategy to a tenofovir-2 NRTI regimen (particularly those containing ddI) should used with caution, especially in those with previous RT mutations.</td>
</tr>
</tbody>
</table>
### Interaction

<table>
<thead>
<tr>
<th>Interaction</th>
<th>Dosing Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abacavir, 3TC, tenofovir</td>
<td>Simplification strategy to abacavir-3TC-tenofovir should be used with caution, especially in those with previous RT mutations.</td>
</tr>
</tbody>
</table>

#### b. INCREASED TOXICITY

<table>
<thead>
<tr>
<th>Didanosine</th>
<th>Reduce didanosine dose to 250 mg QD when administering with tenofovir. Monitor response, including CD4 counts, particularly after 6 months of therapy.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Didanosine Paradoxical ↓ in CD4 counts in patients virally suppressed on combination. Using 250 mg ddl with TDF may lead to partial improvement in CD4 counts.</td>
<td>Reduce didanosine dose to 250 mg QD when administering with tenofovir. Monitor response, including CD4 counts, particularly after 6 months of therapy.</td>
</tr>
<tr>
<td>Case reports of pancreatitis, fatal lactic acidosis, and/or renal failure reported with combination of didanosine and tenofovir.</td>
<td>Monitor for toxicity.</td>
</tr>
</tbody>
</table>

NB: The European Medicines Agency (EMEA) issued a statement on March 3, 2005, alerting health care providers to safety and efficacy concerns regarding tenofovir and didanosine coadministration. In its statement, the EMEA noted that using didanosine 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 EMEA 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 didanosine and tenofovir together was “strictly necessary”, subjects should be closely monitored for didanosine-related side effects as well as regimen efficacy.


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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