Review of tenofovir-emtricitabine

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Abstract: Highly active antiretroviral therapy has significantly reduced HIV-related morbidity and mortality. Increasingly, fixed-dose antiretroviral combinations with equal or greater potency than traditional antiretrovirals, along with fewer side effects, reduced toxicity, and simplified dosing convenience are being utilized. Tenofovir-emtricitabine (TDF-FTC) represents one of the more recent fixed-dose combinations. In combination with either a ritonavir-boosted protease inhibitor or a non-nucleoside reverse transcriptase inhibitor, TDF-FTC is a preferred choice in recent treatment guidelines on the basis of demonstrated potency in randomized clinical trials, one-pill-a-day dosing convenience, and relatively low toxicity. In addition, the drug is active against hepatitis B virus. Caution must be exercised in patients with renal insufficiency, or when the drug is used with certain other drugs. This manuscript reviews the use of TDF-FTC in the treatment of HIV.

Keywords: tenofovir, emtricitabine, Truvada, TDF, FTC, antiretroviral agent

Introduction

Health care practitioners and researchers have been fighting human immunodeficiency virus (HIV) infection for over two decades. During this time, significant progress has been made in understanding the pathogenesis, clinical presentation, and epidemiology of the disease. The advent of antiretroviral therapy has significantly improved the prognosis and quality of life of persons living with HIV. Currently, over 20 antiretroviral drugs have been approved by the Food and Drug Administration (FDA) for the treatment of HIV infection. These agents are classified into: (a) nucleoside/nucleotide reverse transcriptase inhibitors (NRTI/NtRTI), (b) non-nucleoside reverse transcriptase inhibitors (NNRTI), (c) protease inhibitors (PI), and (d) fusion inhibitors. Despite the increased number of choices, issues of adherence, tolerability, long-term toxicity, and drug resistance remain to be some of the major challenges in the management of HIV. To address these problems, advances have been made in the development of novel agents and fixed-dose combination treatment regimens with greater potency, lower toxicity, and improved convenience for patients.

Central among the factors affecting adherence and compliance in the treatment of HIV/AIDS are antiretroviral dosing frequency and pill burden. The effort toward reduced dosing frequency and pill burden has led to the first FDA-approved, once a day, single pill treatment for HIV that contains three antiretroviral medications – efavirenz, tenofovir, and emtricitabine. However, many patients must continue to take more complicated and toxic HIV therapeutic regimens due to drug intolerance or drug resistance (Masquelier et al 2005; Ross et al 2007). Tenofovir disoproxil fumarate-emtricitabine (TDF-FTC) is a once-daily, fixed-dose NtRTI/NRTI combination that has demonstrated efficacy in well-designed clinical trials with good follow up (Pozniak et al 2005; Gallant et al 2006; Pozniak et al 2006). TDF-FTC combines the benefits of less toxicity, dosing simplicity, and favorable pharmacokinetic properties (Table 1). This article will review the current use of this versatile NtRTI/NRTI combination in the management of HIV patients.

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Table 1 Pharmacokinetic characteristics of once-a-day NRTI agents

Agent	Meal/food effect	Oral bio-availability	Serum half-life	Intracellular half-life	Elimination and metabolism
Emtricitabine (FTC)	No regard to meal	93%	10 h	>20 h	Renal excretion; dosage adjustment in renal insufficiency
Lamivudine (3TC)	No regard to meal	86%	5–7 h	18–22 h	Renal excretion; dosage adjustment in renal insufficiency
Abacavir/Lamivudine (ABC/3TC)	No regard to meal (Alcohol increases ABC to 41%, no regard to meal)	83%/86%	1.5 h/5–7 h	12–26 h/18–22 h	Metabolized by alcohol dehydrogenase and glucuronyl transferase; renal excretion of metabolites 82%; not for patients with CrCl <50 mL/min
Emtricitabine/Tenofovir (FTC/TDF)	No regard to meal	93%/25% fasting, 39% with high fat meal	10 h/17 h	>20 h/ >60 h	Renal excretion; dosage adjustment in renal insufficiency; not for patients with CrCl <30 mL/min
Didanosine (ddI)	Level decreases 55%; take ½ h before or 2 h after meal	30%–40%	1.5 h	>20 h	Renal excretion 50%; dosage adjustment in renal insufficiency
Tenofovir disoproxil fumarate (TDF)	no regard to meal	25% fasting, 39% with high-fat meal	17 h	>60 h	Renal excretion 50%; dosage adjustment in renal insufficiency; not for patients with CrCl <30 mL/min
Abacavir/Lamivudine ABC	No regard to meal (Alcohol increases ABC to 41%, no regard to meal)	83%	1.5 h	12–26 h	Metabolized by alcohol dehydrogenase and glucuronyl transferase; renal excretion of metabolites 82%

Adopted from DHHS guidelines, Table 11, May 4, 2006.
(US Department of Health and Human Services, Panel on Clinical Practice for Treatment of HIV infection. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Version May 4, 2006. Available at: http://www.aidsinfo.nih.gov/contentfiles/adultand adolescentgl.pdf. Accessed May 16, 2006)

To better understand the characteristics of TDF-FTC, it is essential to examine its components, TDF and FTC (Table 2).

Tenofovir disoproxil fumarate (TDF, Viread®)

Approved by the FDA in 2001, TDF (the ester prodrug of tenofovir) is hydrolyzed to tenofovir intracellularly and phosphorylated to the active metabolite, tenofovir diphosphate (Lyseng-Williamson et al 2005). Tenofovir is a nucleotide analog of deoxyadenosine monophosphate, with activity against HIV-1, -2 and Hepatitis B virus (HBV) (Mulato and Cherrington 1997; Robbins et al 1998). Because of its long half-life (17 hours), it is administered once daily with other antiretroviral drugs. Several clinical trials indicated that TDF is highly potent in both treatment-naïve and experienced patients at reducing HIV viral load significantly (Squires et al 2003; Gallant et al 2004; Negredo et al 2004). It was also shown to be effective as an alternative antiviral agent during treatment failure or drug toxicity among treatment-experienced patients (Lyseng-Williamson 2005). It can be taken without regard to food consumption, but is absorbed 39% when taken with a fatty meal compared to 25% when administered before a meal (fasting) (Viread package insert 2005).

TDF is excreted unchanged by the kidneys; thus, renal tubular toxicity is an important but uncommon side effect (Ristig et al 2002; Barrios et al 2004; James et al 2004; Murphy et al 2003; Schaaf et al 2003). Caution and dose adjustment is recommended in renal insufficiency/failure (Viread package insert 2005). TDF is not metabolized by cytochrome P450 enzymes, so little potential for interactions with drugs metabolized by these enzymes exists. TDF induces little or no mitochondrial toxicity or dyslipidemia. Other occasional adverse reactions include nausea, diarrhea, vomiting, rash, and flatulence.

Emtricitabine (FTC, Emtriva®)

Emtricitabine, FTC is a fluorinated derivative of lamivudine (3TC), an analog of deoxycitidine, which is active against HIV-1, -2 and hepatitis B virus. It has been approved by the FDA for use since 2003 and is currently recommended as part of an initial preferred HIV treatment regimen (Department of Health and Human Services 2006). As compared to 3TC, FTC has a longer half-life, higher oral bioavailability, and slightly greater potency *in vitro*, although the clinical significance of this remains unclear (Schinazi et al 1992; Frampton et al 2005). Studies indicate that FTC is efficacious in combination with other antiretrovirals in reducing HIV viral loads in both treatment-naïve and experienced patients (Molina et al 2000; Benson et al 2004; Saag et al 2004; Molina et al 2005). FTC can be taken without regard to food consumption and is completely eliminated via the kidneys, so dosage adjustment is required in case of renal insufficiency (Sax et al 2007). Potential drug interactions and toxicity, including mitochondrial toxicities and dyslipidemias, are nearly absent. The most common side effects include headache, insomnia, diarrhea, nausea, vomiting, and rash (Benson et al 2004; Saag et al 2004). FTC may cause skin hyperpigmentation of the palms and soles in African and African American patients.

Tenofovir-emtricitabine (Truvada®)

TDF-FTC is a once daily treatment composed of TDF and FTC to be used in combination with other antiretroviral drugs. The TDF-FTC co-formulation contains 300 mg of TDF and 200 mg of FTC administered orally in one tablet that has

Table 2 Characteristics of tenofovir and emtricitabine

Characteristics	TDF	FTC	TDF-FTC[a]
Generic/Brand name	Tenofovir DF/ Viread	Emtricitabine/Emtriva	Truvada
Manufacturer	Gilead Sciences	Gilead Sciences	Gilead Sciences
FDA approval date	October 2001	July 2003	August 2004[a]
Supplied as	300 mg tabs	200 mg caps	300 mg TDF + 200 mg FTC in one tab
Recommended dose	300 mg daily	200 mg daily	1 tab daily
Administration	Orally with or without food	Orally with or without food	Orally with or without food
Median fasted oral bioavailability (range)	25 (not calculated – 45)	93 (83.1–106.4)	25 for TDF 92 for FTC
Food effect	None	None	None
Toxicity	Minimal GI intolerance Nephrotoxicity	Minimal Hyperpigmentation of palm and sole	Minimal GI intolerance Hyperpigmentation Nephrotoxicity

[a]Obtained accelerated approval in the US.

bioavailability equivalence to the single drug formulations. TDF and FTC have synergistic antiviral effects on HIV-1 and HIV-2 (Louie et al 2003; Gilead Sciences 2006). The co-formulation is considered efficacious therapy that can be used in multi-drug HIV treatment regimens (Gallant et al 2006; Pozniak et al 2006). Recently, the US Department of Health and Human Services listed TDF and FTC among the preferred options as part of NNRTI or PI based antiviral combination therapy (Department of Health and Human Services 2006; Hammer et al 2006). TDF-FTC with the NNRTI efavirenz represents the most simplified antiretroviral dosing schedule yet, consisting of two pills or a single three-drug, fixed-dose combination tablet (Atripla®) once a day. When combined with one of three currently recommended ritonavir-boosted PIs, the daily pill burden is a total of 4 or 5 pills. The only other preferred NRTI fixed-dose combination pill, zidovudine (ZDV) +3TC (Combivir®), is given twice a day. Other once-a-day NRTI combinations include fixed-dose abacavir + lamivudine (Epzicom®) and didanosine with either TDF or stavudine (D4T) extended release. Abacavir + lamivudine, while efficacious and well tolerated, has somewhat less clinical trial data supporting its use and at this time remains an alternate recommendation in guidelines. Didanosine combined with either TDF or D4T extended has a higher incidence of toxicity and is not recommended as first-line therapy (Department of Health and Human Services 2006; Hammer et al 2006).

TDF-FTC efficacy

Gilead study 934 was the pivotal efficacy trial for the TDF-FTC combination (Pozniak et al 2006). This randomized, open-label, noninferiority trial enrolled 517 antiretroviral-naïve, HIV-infected patients to receive either TDF + FTC and efavirenz or ZDV + 3TC and efavirenz. The primary endpoint was the proportion of patients with an HIV RNA level <400 copies/mL in patients without baseline non-nucleoside resistance. Through week 96, significantly more patients receiving TDF + FTC achieved and maintained an HIV RNA level <400 copies/mL (75% vs 62%). The TDF + FTC group also demonstrated a significantly greater increase in CD4+ lymphocyte counts (270 vs 237 cells/mm^3; $p = 0.036$).

Another clinical trial, Gilead 903, a randomized, placebo-controlled study, compared TDF or D4T in combination with 3TC and efavirenz in 602 treatment-naïve subjects. This study demonstrated equivalence in the percentage of subjects with HIV RNA <50 copies/mL at week 48 and through 144 with less lipoatrophy and more favorable lipid profiles in the TDF arm (Gallant et al 2004). In treatment-experienced patients, the TDF-FTC is commonly used as guided by drug resistance testing, but the relative benefit of the combination relative to other NRTI/NtRTI choices is difficult to gauge and will depend on many factors, including HIV genotypic or phenotypic susceptibility scores, drug interactions, and compliance. It is well documented that 3TC benefits patients with the RT M184V/I mutation that are incompletely suppressed virologically, possibly as a result of impairing viral fitness or residual virologic activity, and likely this holds true of FTC as well.

Therapeutic use of TDF-FTC among special populations

No efficacy differences have been identified between male and female patients (Gilead Sciences 2006). Sufficient data is not available to examine differences among different races and ethnic groups and geriatric populations. Because both TDF and FTC are excreted via the kidneys, modification of TDF-FTC dosage and special caution is necessary when treating patients with renal impairments (Table 3) (Gilead Sciences 2006; Bartlett and Gallant 2005). Data on dosing in patients with liver impairment is limited; however, no dosing adjustment is recommended (Gilead Sciences 2006).

TDF and FTC are both active against HBV in vitro, in case series (Benhamou et al 2003), and in a small controlled clinical trial with HIV-HBV coinfected subjects (Peters MG et al 2006), but are not approved for that indication. While FTC has no activity against lamivudine-resistant HBV strains, in HIV co-infected patients with a positive HBeAg, the inclusion of TDF in the HIV regimen resulted in a significant reduction of viral load, including those with lamivudine-resistant strains (Nelson et al 2003; Dore et al 2004). TDF also may be active against strains of HBV resistant to the NtRTI adefovir and be more potent as well (Qi et al 2007; Lacombe et al 2007). In its most recent guideline, the American Association for the Study of Liver Disease (AASLD) has also included TDF and FTC as one of the drugs that may be used to treat HIV-HBV co-infected patients (Benhamou 2006; Lok and McMahon 2007). While the efficacy and safety of TDF-FTC has not been thoroughly studied in the treatment of HIV-HBV co-infection, several studies have indicated that discontinuation of TDF-FTC in HBV-infected patients may result in severe and acute exacerbation or flare up of the hepatitis (Bessesen et al 1999; Bartlett and Gallant 2005). Liver function tests should be monitored for at least several months in HIV/HBV co-infected patients who are suspended from treatment with TDF-FTC. Because of the risk of HIV resistance with two-drug therapy, if co-infected

Table 3 TDF, FTC and TDF-FTC dosing in renal insufficiency and hepatic failure

Drug	Standard dose	Dose for renal insufficiency/ failure	Dose in hemodialysis	Hepatic failure
TDF	300 mg qd	CrCl 30–49: 300 mg q 48 h 10–29: 300 mg 2×/wk<10: No recommendation	300 mg/wk	Standard dose
FTC	200 mg qd	CrCl 30–49: 200 mg q 48 h 15–29: 200 mg q 72 h <15: 200 mg q 96 h	200 mg q96 h	No recommendation
Truvada (TDF/FTC)	300 mg/200 mgqd	CrCl >50 standard dose qd 30–49: every 48 h <30 should not be administered	Not administered	Standard dose

(Bartlett and Gallant 2005; Gilead Sciences 2006)

patients require treatment, other agents such as adefovir or pegylated interferon should be used.

TDF-FTC is excreted in breast milk and should not be used while nursing (Gilead Sciences 2006). The effects of TDF-FTC in pregnant and nursing mothers need to be investigated further in light of its future use.

Resistance and cross-resistance

Resistance to TDF is conferred by the reverse transcriptase (RT) K65R and/or K70E mutations (Van Rompay et al 2007). K65R can be selected by TDF as well as the NRTIs abacavir and didanosine. This mutation is relatively uncommon. In antiretroviral-naïve patients, there is little baseline resistance to TDF. More than two of certain thymidine analog mutations (TAMS – RT M41L, L210W, and T215Y/F) confer that resistance to TDF may be present. TDF does not select for TAMs. The RT M184V/I mutation is selected by both FTC and 3TC, though perhaps slightly less readily by the former, and leads to complete cross-resistance between the two. Interestingly, the M184V/I mutation can partially re-sensitize HIV that contains TAMs or the K65R mutation to TDF. Using FTC or 3TC with TDF may result in a somewhat higher barrier to drug resistance than seen with TDF alone, though several triple NRTI studies using TDF with FTC or 3TC have demonstrated that this theoretical benefit has limits.

A recent literature review indicated that resistance to FTC-TDF is relatively infrequent (Muñoz de Benito and Arribas Lopez 2006). Among the two Gilead clinical trials, a significant difference was seen in the proportion of patients receiving experiencing virologic rebound on therapy that developed the K65R mutation, with 22% (8 of 36) of patients in the 903 study and no patients in the 934 study developing the mutation (Pozniak et al 2006). The reason for this discrepancy is unclear, though follow up in 903 was longer. The incidence of M184V/I in the TDF arm was 39% and 14%, respectively, but since the incidence of virologic rebound was small, these do not represent large numbers.

Toxicity and adverse reactions

TDF-FTC is generally well tolerated, with few side effects as noted above for the individual compounds. Lactic acidosis and hepatomegaly with steatosis, including fatal cases, have been reported with most other nucleosides but have not been reported to occur with TDF-FTC, to our knowledge (Gilead Sciences 2006).

TDF and FTC are principally eliminated via the kidneys. Like the known nephrotoxic NtRTIs cidofovir and adefovir, TDF is extracted from the blood plasma by the human renal organic anion transporters (hOAT1 and hOAT3), which has suggested the possibility of renal tubular toxicity (Uwai et al 2007). While the data concerning the clinical relevance on this are somewhat inconsistent (Mocroft et al 2007; Gayet-Ageron et al 2007; Pozniak et al 2006; Gallant et al 2007), it appears that renal tubular toxicity, and occasionally Fanconi's syndrome (renal tubular injury with severe hypophosphatemia, phosphoturia, and glycosuria), serious hyperkalemia (Shepp et al 2007), or acute interstitial nephritis may develop with TDF or TDF-FTC use. The majority of these cases occurred in patients with underlying systemic vascular insult, low glomerular filtration rates (GFR)/ chronic renal failure, or in patients taking nephrotoxic agents. Certain genetic haplotypes may be associated in some cases (Izzedine et al 2006), though a number of cases have occurred in patients without identifiable risk factors.

Because certain protease inhibitors, including lopinavir and atazanavir, increase the serum levels of TDF by as much as 25%, this could be a risk factor for nephrotoxicity (Kiser et al 2007; Goicoechea et al 2007), and extra caution is advised. The drug should be used only with great caution in patients with reduced GFR. All HIV infected patients, particularly those on TDF, should have baseline and yearly determination of GFR using either the Cockcroft-Gault or modification of diet in renal disease (MDRD) method, as well as regular assessments of serum blood urea nitrogen and creatinine. Consideration should be given to monitoring serum phosphate in those on TDF as well. Significant GFR or serum phosphate decline should prompt further evaluation and strong consideration for discontinuation of TDF (Ristig et al 2002; Murphy et al 2003; Schaaf et al 2003; Barrios et al 2004; James 2004; Gilead Sciences 2006). It is not well-elucidated if TDF-induced renal tubular toxicity routinely results in phosphaturia or glycosuria, so the absence of these cannot be relied upon to exclude a role for TDF in a patient's renal failure.

Subclinical renal phosphate wasting could possibly contribute to a decrease in bone mineral density that was reported in a study conducted among treatment-naïve patients who were treated with TDF in Gilead 903 (Cassetti et al 2006, 2007). A decrease in bone mineral density at the lumbar spine and hip, especially between weeks 24 and 48, was evident but was non-progressive through 288 weeks. Thus, monitoring of bone mineral density should be considered in patients with history of, or risk factors for, pathologic fractures. To the knowledge of the authors, no study has examined the benefit of calcium and vitamin D supplementation or bisphosponates in this setting.

Use of TDF-FTC has been associated with fewer overall adverse effects than D4T-3TC or ZDV-3TC. Compared with ZDV, TDF is associated with a lower frequency of anemia (4% vs 9%, respectively; $p = 0.02$) (Gallant et al 2006), and compared with D4T, TDF is associated with fewer lipid abnormalities.

Both TDF and abacavir containing regimens are associated with less severe side effects or improvements in lipoatrophy, a reduction in subcutaneous fat tissue, particularly in the face and extremities. This condition may result from mitochondrial toxicity induced in particular by the thymidine analog NRTIs, ZDV and D4T. In Gilead 934, limb fat, measured by whole-body DEXA at weeks zero and 96, was significantly greater in the TDF + FTC + efavirenz group versus the ZDV + 3TC + efavirenz group (7.7 vs 5.5 kg; $p < 0.001$) (Pozniak et al 2006). A similar lipoatrophy benefit with TDF was observed in an analysis restricted to African or African American study participants (Gallant et al 2007). An interesting twist to this story was suggested by AIDS Clinical Trial Group (ACTG) study 5142, which confirmed greater limb fat loss with D4T as compared with AZT, and ZDV as compared with TDF containing regimens; but in addition, NNRTI containing regimens were associated with greater fat loss than PI containing regimens, independent of which NRTi/NtRTI was used (Haubrich et al 2007). The mechanism for an apparent lipoatrophy-potentiating effect of NNRTIs on NRTIs is not understood at this time, but this study should prompt further investigation.

Drug interactions

It is assumed that drug interaction for TDF-FTC is the same when administered combined or dosed alone as TDF or FTC. Any medications that reduce renal function may increase concentration of FTC and TDF. No drug interactions with clinical consequences are known for FTC. As mentioned above, co-administration of TDF with certain protease inhibitors, including atazanavir, lopinavir/ritonavir, and darunavir (TMC-114)/ritonavir (Hoetelmans et al 2007) results in increased plasma levels of TDF and, in the case of atazanavir and lopinavir/ritonavir, reduced protease inhibitor troughs. While no dose adjustment is recommended when TDF is used with these drugs (Bartlett and Gallant 2005; DHHS 2006), in cases where baseline protease resistance mutations have modestly raised the concentration of the drug required to inhibit the virus, this effect of TDF could be significant. Atazanvir should always be ritonavir boosted (atazanavir 300 mg should be boosted with ritonavir 100 mg) when used with TDF.

TDF should be used very cautiously with didanosine due to increased rates of adverse reactions including peripheral neuropathy and pancreatitis. This is likely a result of a drug interaction resulting in a 40%–50% increase in plasma didanosine levels (Pruvost et al 2005) and/or intracellular drug interactions. In addition, use of TDF with didanosine has also been associated with paradoxical CD4 declines or less than robust CD4 increases in some, but not all studies (Barrios 2005; Karrer et al 2005; Torti et al 2007). These results are reminiscent of those seen in studies combining didanosine with hydroxyurea. If co-administration of didanosine and TDF is necessary, didanosine dose should be adjusted and patients should be closely monitored for didanosine-related adverse reactions. The recommended didanosine dose for patients weighing >60 kg in this setting

Table 4 Advantages and disadvantages of TDF-FTC

	TDF-FTC
Advantages	• Potent antiretroviral activity • No food effect • Longer intracellular half-life than 3TC • Once-daily regimen • Effective against HBV • Well tolerated • Avoid or delay Thymidine Analog Mutations (TAMs) • Low potential for mitochondrial toxicity
Disadvantages	• Rapid selection of 184V RT mutation in non-suppressive regimen with substantial loss of activity • Rapid selection of 184V RT • Risk of Abacavir (ABC) and Didanosine (ddI) cross-resistance after failure (K65R) Tenofovir disoproxil fumarate (TDF) interaction to decrease levels of ATV (use ATV/r) • In general, Non Nucleoside Reverse Transcriptase Inhibitors (NNRTIs) may cause hepatotoxicity with elevated transaminases. Reported rates of grads 3–4 hepato toxicity are 8%–15%, and highest with NVP (Martin-Carbonero et al 2003; Law et al 2003; Spengler et al 2002)

is 250 mg; however, there is no adequate information for patients weighing below 60 kg (Gilead Sciences 2006).

Conclusion

There is sufficient data to recommend the use of TDF-FTC in the treatment of HIV. It is recommended as a preferred and alternative treatment of choice in both treatment-naïve and experienced patients. In addition to its demonstrated efficacy, TDF-FTC also provides significant advantages in terms of few side effects, low long-term toxicity, once daily dosing, few drug interactions, useful anti-HBV activity, and a relatively high genetic barrier relative to other NRTIs/NtRTIs (Table 4). Caution must be exercised in patients with reduced renal function and when the drug is used with certain other antiretrovirals.

References

Barrios A, Gracia-Benayas T, Gonzalez-Lahoz J, et al. 2004. Tenofovir-related nephrotoxicity in HIV-infected patients. *AIDS*, 18:960–3.

Barrios A, Rendon A, Negredo E, et al. 2005. Paradoxical CD4+ T-cell decline in HIV-infected patients with complete virus suppression taking tenofovir and didanosine. AIDS, 19:569–75. Comment in. *AIDS*, 19:1722–3.

Bartlett JG, Gallant JE. 2005. 2005–2006 Medical management of HIV infection. Johns Hopkins Medicine. Health Publishing Business Group.

Benhamou Y. 2006. Treatment algorithm for chronic hepatitis B in HIV-infected patients. *J Hepatol*, 44(1 Suppl):S90–4.

Benhamou Y, Tubia R, Thibault V. 2003. Tenofovir disoproxil fumarate in patients with HIV and lamivudine-resistant hepatitis B virus. *New Engl J Med*, 348:177–8.

Benson CA, Van der Horst C, Lamarca A, et al. 2004. A randomized study of emtricitabine and lamivudine in stably suppressed patients with HIV. *AIDS*, 18:2269–76.

Bessesen M, Ives D, Condreay L, et al. 1999. Chronic active hepatitis B exacerbations in human immunodeficiency virus-infected patients following development of resistance to or withdrawal of lamivudine. *Clin Infect Dis*, 28:1032–5.

Cassetti I, Madruga JVR, Suleiman JMAH, et al. 2006. The safety and efficacy of tenofovir DF in combination with lamivudine and efavirenz through 5 years in antiretroviral-naive patients. 8th International Congress on Drug Therapy in HIV Infection. November 12–16, Glasgow Abstract P152.

Cassetti I, Madruga JV, Suleiman JM, et al. 2007. The safety and efficacy of tenofovir DF in combination with lamivudine and efavirenz through 6 years in antiretroviral-naive HIV-1-infected patients. *HIV Clin Trials*, 8:164–72.

Department of Health and Human Services-Office of AIDS Advisory Council. May 2006. Guidelines for the use of antiretroviral agents for HIV-1 infected adults and adolescents. Bethesda, MD. Accessed September 25, 2006. URL: http://aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf

Dore GJ, Cooper DA, Pozniak AL, et al. 2004. Efficacy of tenofovir disoproxil fumarate in antiretroviral therapy-naive and -experienced patients co-infected with HIV-1 and hepatitis B virus. *J Infect Dis*, 189:1185–92.

Frampton JE, Perry CM. 2005. Emtricitabine: a review of its use in the management of HIV infection. *Drugs*, 65:1427–48.

Gallant JE, DeJesus E, Arras JR, et al. 2006. Tenofovir DF, Emtricitabine, and Efavirenz vs Zidovudine, and Efavirenz for HIV. *N Engl J Med*, 354:251–60.

Gallant JE, Staszewski S, Pozniak AL, et al. 2004. Efficacy and safety of tenofovir DF vs stavudine in combination therapy in antiretroviral-naive patients: a 3-year randomized trial. *JAMA*, 292:191–201.

Gallant J, Pozniak A, Staszewski S, et al. 2007. Efficacy and Safety of Tenofovir-containing vs non-Tenofovir-containing Regimens in Black ART-naive Patients. 14th CROI, Los Angeles, CA, February 25–28, 2007. Abst. 505.

Gayet-Ageron A, Ananworanich J, Jupimai T, et al. 2007. No change in calculated creatinine clearance after tenofovir initiation among Thai patients. *J Antimicrob Chemother*, 59:1034–7.

Gilead Sciences. Full prescribing information, Truvada. Accessed September 25, 2006 at http://www.truvada.com/fpi.pdf

Goicoechea M, Liu S, Best B, et al. 2007. Increased renal impairment in patients receiving TDF + PI vs TDF + NNRTI 14th CROI, Los Angeles, CA, February 25–28, 2007. Abst. 835.

Hammer SM, Saag MS, Schechter M, et al. 2006. Treatment for adult HIV infection: 2006 recommendations of the International AIDS Society-USA panel. *JAMA*, 296:827–43.

Haubrich RH, Riddler S, DiRienzo G, et al. 2007. Metabolic Outcomes of ACTG 5142: A Prospective, Randomized, Phase III Trial of NRTI-, PI-, and NNRTI-sparing Regimens for Initial Treatment of HIV-1 Infection. 14th CROI, Los Angeles Abst. 38.

Hoetelmans RM, Marien K, De Pauw M, et al. 2007. Pharmacokinetic interaction between TMC114/ritonavir and tenofovir disoproxil fumarate in healthy volunteers. *Br J Clin Pharmaco* [in press].

Izzedine H, Hulot JS, Villard E, et al. 2006. Association between ABCC2 gene haplotypes and tenofovir-induced proximal tubulopathy. *J Infect Dis*, 194:1481–91.

James CW, Steinhaus MC, Szabo S, et al. 2004. Tenofovir-related nephrotoxicity: case report and review of the literature. *Pharmacotherapy*, 24:415–18.

Karrer U, Ledergerber B, Furrer H, et al. 2005. Dose-dependent influence of didanosine on immune recovery in HIV-infected patients treated with tenofovir. *AIDS*, 19:1987–94.

Kiser JJ, Carten ML, Aquilante CL, et al. 2007. The effect of lopinavir/ritonavir on the renal clearance of tenofovir in HIV-infected patients. *Clin Pharmacol Ther* [In press].

Lacombe K, Boelle PY, Gozlan J, et al. 2007. Hepatitis B virus plasma dynamics in HIV/HBV-co-infected patients: significant difference in the anti-viral activity of adefovir and tenofovir. 14th Conference on Retroviruses and Opportunistic Infections. Los Angeles, February 25–28, Abstract 945 (poster).

Law WP, Dore GJ, Duncombe CJ, et al. 2003. Risk of severe hepatotoxicity associated with antiretroviral therapy in the HIV-NAT Cohort, Thailand, 1996–2001. *AIDS*, 17:2191–9.

Lok ASF and McMahon B. 2007. Chronic Hepatitis. AASLD Practice Guidelines. *Hepatology*, 45:507–39. Accessed 17 June 2007. URL: https://www.aasld.org/eweb/docs/chronichep_B.pdf

Louie M, Hogan C, Hurley A, et al. 2003. Determining the antiviral activity of tenofovir disoproxil fumarate in treatment-naive chronically HIV-1-infected individuals. *AIDS*, 17:1151–6.

Lyseng-Williamson KA, Reynolds NA, Plosker GL. 2005. Tenofovir disoproxil fumarate: a review of its use in the management of HIV infection. *Drugs*, 65:413–32.

Mocroft A, Kirk O, Gatell J, et al. 2007. Chronic renal failure among HIV-1-infected patients. *AIDS*, 21:1119–27.

Martin-Carbonero L, Núñez M, Gonzãlez-Lahoz J, et al. 2003. Incidence of liver injury after beginning antiretroviral therapy with efavirenz or nevirapine. *HIV Clin Trials*, 4:115–20.

Masquelier B, Bhaskaran K, Pillay D, et al. 2005. Prevalence of transmitted HIV-1 drug resistance and the role of resistance algorithms; data from seroconverters in the CASCADE collaboration from 1987 to 2003. *J Acquir immunie Defic Syndr*, 40:505–11.

Molina JM, Ferchal F, Rancinan C, et al. 2000. Once-daily combination therapy with emtricitabine, didanosine, and efavirenz in human immunodeficiency virus-infected patients. *J Infect Dis*, 182:599–602.

Molina JM, Journot V, Morand-Joubert L, et al. 2005. Simplification therapy with once-daily emtricitabine, didanosine, and efavirenz in HIV-1-infected adults with viral suppression receiving a protease inhibitor-based regimen: a randomized trial. *J Infect Dis*, 191:830–9.

Mulato AS and Cherrington JM. 1997. Anti-HIV activity of adefovir (PMEA) and PMPA in combination with antiretroviral compounds: in vitro analyses. *Antiviral Res*, 36:91–7.

Munoz de Benito RM, Arribas Lopez JR. 2006. Tenofovir disoproxil fumarate-emtricitabine coformulation for once-daily dual NRTI backbone. *Expert Rev Anti Infect Ther*, 4:523–35.

Murphy MD, O'Hearn M, Chou S. 2003. Fatal lactic acidosis and acute renal failure after addition of tenofovir to an antiretroviral regimen containing didanosine. *Clin Infect Dis*, 36:1082–5.

Negredo E, Molto J, Munoz-Moreno JA, et al. 2004. Safety and efficacy of once-daily didanosine, tenofovir and nevirapine as a simplification antiretroviral approach. *Antivir Ther*, 9:335–42.

Nelson M, Portsmouth S, Stebbing J, et al. 2003. An open-label study of tenofovir in HIV-1 and Hepatitis B virus co-infected individuals. *AIDS*, 17:F7–10.

Peters MG, Andersen J, Lynch P, et al. 2006. Randomized controlled study of tenofovir and adefovir in chronic hepatitis B virus and HIV infection: ACTG A5127. *Hepatology*, 44:1110–16.

Pozniak AL, Gallant JE, DeJesus E, et al. 2005. Superior outcome for tenofovir DF, emtricitabine and efavirenz compared to fixed dose zidovudine/lamivudine and efavirenz in antiretroviral naïve patients. Presented at the 3rd IAS Conference on Pathogenesis and Treatment, Rio de Janeiro, July 24–27, Abstract.

Pozniak AL, Gallant JE, DeJesus E, et al. 2006. Tenofovir disoproxil fumarate, emtricitabine, and efavirenz versus fixed-dose zidovudine/lamivudine and efavirenz in antiretroviral-naive patients: virologic, immunologic, and morphologic changes – a 96-week analysis. *J Acquir Immune Defic Syndr*, 43:535–40.

Pruvost A, Negredo E, Benech H, et al. 2005. Measurement of intracellular didanosine and tenofovir phosphorylated metabolites and possible interaction of the two drugs in human immunodeficiency virus-infected patients. *Antimicrob Agents Chemother*, 49:1907–14.

Qi X, Xiong S, Yang H, et al. 2007. In vitro susceptibility of adefovir-associated hepatitis B virus polymerase mutations to other antiviral agents. *Antivir Ther*, 12:355–62.

Ristig MB, Crippin J, Aberg JA, et al. 2002. Tenofovir disoproxil fumarate therapy for chronic hepatitis B in human immunodeficiency virus/hepatitis B virus-co-infected individuals for whom interferon-alpha and lamivudine therapy have failed. *J Infect Dis*, 186:1844–7.

Robbins BL, Srinivas RV, Kim C, et al. 1998. Anti-human immunodeficiency virus activity and cellular metabolism of a potential produrg of the acyclic nucleoside phosphonate 9-R-(2- phoxyosphonomethoxypropyl) adeline (PMPA),Bis (isopropyloxymethylcarbonyl)PMPA. *Antimicrob Agents Chemother*, 42:612–17.

Ross L, Lim ML, Liao Q, et al. 2007. Prevalence of antiretroviral drug resistance and resistance-associated mutations in antiretroviral therapy-naïve HIV-infected individuals from 40 United States cities. *HIV Clinical Trial*, 8:1–8.

Saag MS, Cahn P, Raffi F, et al. 2004. Efficacy and safety of emtricitabine vs. stavudine in combination therapy in antiretroviral-naive patients: a randomized trial. *JAMA*, 292:180–9.

Sax PE, Gallant JE, Klotman PE. 2007. Renal safety of tenofovir disoproxil fumarate. *AIDS Read*, 17:90–2, 99–104, C3.

Schinazi RF, McMillan A, Cannon D, et al. 1992. Selective inhibition of human immunodeficiency viruses by racemates and enantiomers of cis-5-fluoro-1-[2-(hydroxymethyl)-1,3-oxathiolan-5-yl]cytosine. *Antimicrob Agents Chemother*, 36:2423–31.

Schaaf B, Aries SP, Kramme E, et al. 2003. Acute renal failure associated with tenofovir treatment in a patient with acquired immunodeficiency syndrome. *Clin Infect Dis*, 37:e41–3.

Shepp DH, Curtis S, Rooney JF. 2007. Causes and consequences of hypokalemia in patients on tenofovir disoproxil fumarate. *AIDS*, 21:1479–81.

Spengler U, Lichterfeld M, Rockstroh JK. 2002. Antiretroviral drug toxicity – a challenge for the hepatologist? *J Hepatol*, 36:283–94.

Squires K, Pozniak AL, Pierone G Jr, et al. 2003. Tenofovir disoproxil fumarate in nucleoside-resistant HIV-1 infection: a randomized trial. *Ann Intern Med*, 139:313–20.

Torti C, Lapadula G, Barreiro P, et al. 2007. CD4+ T cell evolution and predictors of its trend before and after tenofovir/didanosine backbone in the presence of sustained undetectable HIV plasma viral load. *J Antimicrob Chemother*, 59:1141–7.

Uwai Y, Ida H, Tsuji Y, et al. 2007. Renal transport of adefovir, cidofovir, and tenofovir by SLC22A family members (hOAT1, hOAT3, and hOCT2). *Pharm Res*, 4:811–15.

Viread package insert. Accessed 1 September 2006. URL: http://www.hivandhepatitis.com/hiv_and_aids/viread2005.pdf

Van Rompay KK, Johnson JA, Blackwood EJ, et al. 2007. Sequential emergence and clinical implications of viral mutants with K70E and K65R mutation in reverse transcriptase during prolonged tenofovir monotherapy in rhesus macaques with chronic RT-SHIV infection. *Retrovirology*, 4:25.