"One pill, once daily": what clinicians need to know about Atripla™

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Abstract: As the number of persons chronically prescribed antiretrovirals has grown and the realization that antiretrovirals are required to be continued for life, pharmaceutical manufacturers have developed new classes of agents, improved the pharmacokinetics of marketed products through dosing reformulations, and in an effort to maximize success with respect to adherence, compiled into a single dosing unit all necessary elements for an antiretroviral regimen. Atripla™ represents the first ever fixed-dose combination antiretroviral available. This article reviews currently available data on this agent, the impact of resistance on clinical use and implementation, as well as extensive descriptions of the pharmacokinetics, adverse effects and drug-interactions warranting consideration. Whether beginning in a naïve patient or switching from other regimens for tolerability issues, Atripla™ represents a viable option. Its demonstrated advantages with respect to lipid and hematologic parameters and equivalent incidence of renal toxicity are tempered by the findings of bone mineral density decreases, however. Combining multiple mechanisms of action in a single dosing unit appears to improve efficacy, increase the likelihood for adherence and maintain viral suppression compared to administering these agents independently. It is suggested other pharmaceutical companies assess the potential to replicate this for the remaining antiretrovirals.

Keywords: Atripla™, antiretrovirals, HIV

Introduction

Over a decade ago, highly effective antiretroviral therapies became available (Abramowicz 2006; Hammer et al 2006; Bartlett and Lane 2007) for persons infected with HIV. Correspondingly, the rate of deaths due to AIDS was dramatically reduced and the number of persons living with HIV/AIDS has continued to increase (Palella et al 1998; Egger et al 2002; CDC 2005). As the number of persons chronically prescribed antiretrovirals has grown and the realization that these would be required to be continued for life, pharmaceutical manufacturers have developed new classes of agents, improved the pharmacokinetics of marketed products through dosing reformulations and in an effort to maximize success with respect to adherence, compiled into a single dosing unit all necessary elements for an antiretroviral regimen (Finzi et al 1999; Heeswijk et al 2000; Eron et al 2004; Montfore et al 2005; Goedken and Herman 2005; Moyle et al 2005; Atripla™ 2006; Bartlett et al 2006). Atripla™ (Gilead Sciences, Foster City, CA, and Bristol-MyersSquibb, Newark, NJ, USA) is the first example of a fixed-dose combination (FDC) containing all elements of a preferred antiretroviral regimen as recommended in the most recent HIV treatment guidelines (Atripla™ 2006; Bartlett and Lane 2007). Atripla™ is a FDC tablet containing three antiretroviral medications consisting of the previously US Food and Drug Administration (FDA) approved agents: efavirenz (available as Sustiva®, Bristol-MyersSquibb, Newark, NJ, USA), emtricitabine (available individually as Emtriva®, Gilead Sciences, or in combination with tenofovir diprovoxil fumarate as Truvada®, Gilead Sciences) and

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tenofovir diprovoxil fumarate (abbreviated here as tenofovir, available individually as Viread®, Gilead Sciences, or in combination with emtricitabine as Truvada®) (Young et al 1995; Robbins et al 1998; Truvada® 2006) This article provides a concise summary of this product, the implications for prescribing this agent initially or switching patients to this one tablet once daily regimen who may already be receiving effective therapy and an informative primer for those wishing to learn more about the virus itself as it pertains to the newest approved antiretrovirals.

Review of the microbiology of HIV

The human immunodeficiency virus (HIV) is a retrovirus that is the causative agent of acquired immunodeficiency syndrome (AIDS) (Broder and Gallo 1984). Since its initial discovery major advancements in therapy have been based upon the structure of the virus. Most recently, approval of chemokine receptor antagonists and integrase inhibitors reinforce the need for clinicians to be familiar with a most up-to-date description of the virus' life cycle (Levy 2007) HIV is transmitted by sexual contact, perinatally or by blood (most commonly by contaminated shared needles) (Tirelli et al 1985). The HIV genome is comprised of the structural genes *gag* and *env*, which encode the capsid and matrix proteins, and the glycoproteins gp120 and gp41 respectively. HIV gp120 binds to the CD4 receptor on the surface of T-lymphocytes, and the cell surface proteins CCR5 or CXCR4 act as coreceptors for viral attachment (Chan and Kim 1998). It is the CCR5 chemokine receptor targeted by the FDA-approved drug, maraviroc (Selzentry®, Pfizer, New York, NY, USA) (Bartlett et al 2006) HIV-encoded enzymes include a reverse transcriptase (RT), integrase, and protease (PR) that are encoded by the *pol* gene. The integrase enzyme is the target for raltegravir – the first agent approved in a new class of antiretrovirals (Markowitz et al 2006). The remaining HIV genes (*tat*, *rev*, *vpr*, *nef*, *vif*, and *vpu*) encode non-structural regulatory proteins that facilitate HIV infection and replication and are the targets in ongoing drug discovery (Levy 1993; Sarkar et al 2007). It is the viral RT enzyme which is the target for the antiretroviral agents contained in Atripla™.

Viral replication occurs throughout HIV infection although patients are often asymptomatic (Coombs et al 1989; Ho et al 1989). Treatment with HIV-1 RT inhibitors causes a rapid exponential decrease in plasma levels of virus, reflecting the short half-life of free virus, which has been estimated to be less than 6 hours (Wei 1995; Perelson et al 1996). Antiretroviral therapy-dependent reduction in viral levels results in HIV plasma levels that are often below the detection limit within the first month after initiating (Gulick et al 1997; Hammer et al 1997; Markowitz et al 2006; Bartlett et al 2006). In fact, due to the high likelihood of this precipitous decline shortly after initiating therapy, it is recommended to have patients newly started on antiretrovirals to return for a follow-up to measure viral load within the first 4 weeks (Bartlett and Lane 2007). HIV-1 replication occurs primarily in activated CD4+ T cells, but there is evidence that latent HIV-1 infection can take place in resting CD4+ T cells (Folks et al 1986; Nabel and Baltimore 1987; Chun et al 1995). These infected cells form a stable, long-term reservoir of latent virus in the form of resting memory CD4+ T cells that carry integrated provirus in vivo (Garcia-Blanco and Cullen 1991; Chun et al 1995, 1997). The latently infected CD4+ T lymphocytes are a major barrier for virus eradication and treatment of infection. The latent virus reservoir is, unfortunately, very stable ($t\,½ \geq 43$ months) in patients on therapy (Finzi et al 1999). Thus, a conservative estimate provides that at minimum of 60.8 years of treatment would be required to eradicate this viral reservoir. Therefore, life-long antiviral therapy for all HIV-infected individuals is a necessity.

Atripla™ has two distinct mechanisms for reducing and/or eliminating replicating virus. This aligns with the most recent treatment guidelines approach to effective antiretroviral therapy (see Efficacy section below) (Bartlett and Lane 2007). Efavirenz is an HIV-1 specific non-nucleoside reverse transcriptase inhibitor (NNRTI) that acts as a noncompetitive inhibitor of HIV RT (Young et al 1995). The in vitro susceptibility of efavirenz has been assessed for wild type laboratory and clinical strains of HIV in lymphoblastoid cell lines, peripheral blood mononuclear cells (PBMCs), and macrophage/monocyte cultures and the $IC_{90\text{-}95}$ ranged from 1.7 to 2.5 nM (Atripla™ 2006). The plasma levels required for this and the other two components of Atripla™ to achieve and maintain efficacy are well surpassed as detailed in the pharmacology section below.

A second Atripla™ component is emtricitabine. This synthetic nucleoside analog of cytidine has activity against HIV-1 RT as a nucleoside RT inhibitor (NRTI). It is phosphorylated by cellular enzymes to form emtricitabine 5'-triphosphate (Frampton and Croom 2006). Activated emtricitabine inhibits viral RT by competing with deoxycytidine 5'-triphosphate (a natural substrate), incorporates into nascent viral DNA, resulting in chain termination and cessation of viral replication. The antiviral activity of emtricitabine has been assessed for laboratory and clinical isolates of HIV-1 in lymphoblastoid cell lines (MAGI-CCR5)

and PBMCs and antiviral activity was observed against HIV-1 clades A, B, C, D, E, F, and G (EC_{50} values ranged from 0.007 to 0.075 μM) (Atripla™ 2006).

Tenofovir , the third component of Atripla™, is an acyclic nucleoside phosphonate diester analog of adenosine monophosphate containing a phosphomimetic group. Tenofovir requires initial diester hydrolysis for conversion to tenofovir (a NRTI) and subsequent diphosphorylations by cellular enzymes to form tenofovir diphosphate (Chapman et al 2003; Dando and Wagstaff 2004; Frampton and Croom 2006). This is distinct from the other NRTIs in that those require triphosphorylation in order to become activated. Tenofovir can sometimes found abbreviated as "NtRTI" to distinguish it from the nucleoside based agents if not all grouped together (Bartlett and Lane 2007). Tenofovir disphosphate is the active component that then acts as a competitive inhibitor of the natural substrate (dATP. deoxyadenosine 5'-triphosphate). Like emtricitabine, tenofovir is incorporated into nascent viral DNA and acts as a chain terminator, resulting in the cessation of viral replication. The in vitro activity against laboratory and clinical HIV isolates has been assessed in lymphoblastoid cells lines, primary monocyte/macrophage cells and peripheral blood lymphocytes, and the IC_{50} was determined to be 0.04 to 8.5 mM.

Each active component of Atripla™ inhibits the activity of HIV RT and results in the inhibition of viral replication (Lyseng-Williamson et al 2004; Frampton and Perry 2005) and all demonstrate antiviral activity in vitro against clinical isolates and laboratory strains of HIV-1 in lymphoblastoid cells lines, PBMCs, macrophage/monocyte cell lines (tenofovir and efavirenz only), and MAGI CCR5 cells (emtricitabine only) (Young et al 1995; Truvada® 2006; Sustiva® 2007).

Review of resistance to Atripla™

In an infected person, the HIV population is heterogeneous and the genome is considered to be in a dynamic state (Perelson et al 1996; Charpentier et al 2006). During administration of antiretroviral drugs, selective pressure is applied to the viral genome, and mutations that can lead to or confer resistance to the drug(s) present are selected and amplified (Badri et al 2007). As a result, virus replication in the presence of antiretroviral continues to result in increases in drug resistance in the population. HIV resistance to NNRTIs can require as little as one mutation in the HIV RT enzyme (Sustiva 2007). As the population of HIV infected persons continues to grow and increasing numbers of people are prescribed antiretrovirals, the likelihood HIV drug resistance becomes a global issue that must be considered as new antiretroviral drugs and drug combinations are introduced (Little and Smith 2005). An annual guide to interpreting drug resistance mutations is provided free-of-charge by the International AIDS Society and should be considered as invaluable to those caring for HIV-infected persons (Johnson et al 2007).

This is perhaps of greatest interest in those persons becoming newly infected. Questions arise as to whether or not these individuals are having resistant or relatively naïve virus transmitted. Recent published trends for resistance, using standard assays, a large database (n = 822) and 10 years of results, have proposed a stable 7.7% rate of transmission of resistant virus to newly infected (Yerly et al 2007). Others, albeit smaller cohorts, show HIV being transmitted as resistant virus in 9.1% of newly infected (Wensing et al 2006) Of greater concern is the disparity between current reported rates of resistance in chronically infected persons using a standard versus a new experimental assay. Using an "ultradeep sequencing" assay, an increase in the proportion of persons with detectable resistance mutations rose from 12% to 20% and from 13% to 30% in the International AIDS Society and Stanford databases, respectively (Simen 2007).

These rates fluctuate greatly based on geographic region, which often reflects access to medications. Recently published resistance rates range from lows of 5.5%–7.4% in Africa, East and Southeast Asia, and Latin American to highs of 10.6%–11.4% in Europe and North America (Maglione et al 2007). While some have predicted rates of multidrug resistance decreasing in the coming years (Blower et al 2007), clinicians are still faced with trying to understand what is present today. In order to most appropriately perform this task, it cannot be emphasized enough that current (online sources) geographically appropriate information is required. Even in a country with relatively high rates of antiretroviral usage (USA), variance existed. Overall 11%–13% of samples tested demonstrated resistance to at least one class of drugs, but that even within this one country varied from 8%–13% (Ross et al 2007). The change in resistance rates over this study period, by class of drug, is noteworthy. While NRTI and PI rates remained relatively stable 3%–4% and 2% (no change), respectively, NNRTI rates rose from 2% to 7% (Ross et al 2007). This trend is mimicked by recent data comparing North America with Westerm Europe in that rates of NNRTI resistance rose from 4.4% to 8.7% and from 0% to 3.7%, respectively (Rahim et al 2007). Rates of resistance to the NRTI and PI classes, while increasing only slightly or stabilizing (Rahim et al 2007), will likely only remain as such with continued appropriate use of antiretroviral agents

and early and repeated uses of resistance testing in those on or being considered for therapy.

Resistance patterns for the three components of Atripla™ have been defined by sequencing the RT-encoding gene of HIV clinical isolates that demonstrate reduced susceptibility to each drug in cell culture. These data come primarily from administration of the individual agents with the rate of resistance for persons receiving Atripla™ detailed below. Resistant viral isolates have been found both in vitro and from patients receiving treatment (Atripla™ 2006). Primary mutations for tenofovir include K65R (the signature mutation), T69S, and a combination of three of the following: M41L, D67N, K70R, L210W, T215Y/F, or K219Q/E/N. Mutations observed in isolates that show reduced susceptibility to emtricitabine include M184V/I (signature mutation), and K65R (when selected by other NRTIs). Lastly, mutations found to be associated with efavirenz resistance are K103N (signature mutation), A98G, L100I, K101E/P, V106A, Y181X, Y188X, G190X, P225H, F227L, or M230L (Atripla™ 2006). In general, tenofovir-resistant isolates (K65R) tend be less sensitive to emtricitabine, but are hypersusceptible to efavirenz (Atripla™ 2006).

Two recent studies reported on the development of drug resistance when these agents are administered in combination. Though neither of these studies used the actual Atripla™ formulation, the three elements were used as a regimen. In one (GS-99-934), resistance was observed in 9 of 244 patients (3.7%) (Gallant et al 2006). Of the study participants who developed resistance, all contained NNRTI-associated mutations and two had the M184V mutation (emtricitabine signature mutation). It was interesting that no resistance was associated with the K65R mutation in this study. Furthermore, after 96 weeks, study participants had less overall resistance compared to participants on a combination of two other NRTI drugs (lamivudine and zidovudine) plus efavirenz (McColl et al 2006). No participants receiving the tenofovir containing regimen developed the K65R mutation (signature mutation for tenofovir resistance). In the second study (ACTG 5142), 33% (n = 11/33) and 48% (n = 16/33) of those virologically failing developed resistance to a NRTI or NNRTI component, respectively (Riddler et al 2006). Of the NRTI mutations, 8/11 were found to have M184V and 3/11 developed K65R. The NNRTI signature mutation of K103N was seen in 9/16. Clinicians using resistance testing in persons receiving these agents should be vigilant for these mutations.

Pharmacokinetics

One Atripla™ tablet is bioequivalent to efavirenz 600 mg, emtricitabine 200 mg, and tenfovir diprovoxil fumarate 300 mg after single-dose administration to fasting healthy volunteers (Mathias 2006). The pharmacokinetic properties of the individual agents found in Atripla™ are discussed below.

Emtricitabine

Following oral administration, emtricitabine is rapidly absorbed with peak plasma concentrations occurring at 1–2 hours post-dose. Following multiple dose oral administration to 20 HIV-infected subjects, the steady-state plasma dosing interval was 1.8 ± 0.7 μg/mL (mean ± SD) and the AUC over a 24-hour dosing interval was 10.0 ± 3.0 μg/h/mL. Mean absolute bioavailability is 93%. Emtricitabine has low protein binding (<4%). Following oral administration, approximately 86% of the dose is excreted in the urine (by a combination of glomerular filtration and active tubular secretion), with 13% of the dose excreted as metabolites. The inactive metabolites of emtricitabine include 3'-sulfoxide diastereomers and their glucuronic acid conjugate (Atripla™ 2006).

Tenofovir diprovoxil fumarate

After single dose oral administration of 300 mg tenofovir DF to HIV-infected subjects, maximum serum concentrations were achieved at 1.0 ± 0.4 hours (mean ± SD) and C_{max} and AUC values were 296 ± 90 mg/mL and 2287 ± 685 mg/h/mL, respectively. The oral bioavailability of tenofovir from tenofovir DF in fasted patients is approximately 25%. Protein binding is low (<0.7%). Approximately 70%–80% of the intravenous dose of tenofovir is recovered unchanged in the urine. Tenofovir is eliminated renally by a combination of glomerular filtration and active tubular secretion (Atripla™ 2006).

Efavirenz

Following 600 mg once-daily administration, C_{max} at steady state was 12.9 ± 3.7 μM (mean ± SD), C_{min} was 5.6 ± 3.2 μM and AUC was 184 ± 73 μM/h. Efavirenz is highly protein bound (>99%) to human plasma proteins, predominantly albumin. Efavirenz is metabolized primarily by CYP2B6 and to a lesser extent, CYP3A4 and it has been demonstrated that efavirenz induces predominantly CYP3A4. Fourteen to 24% of efavirenz dose is excreted renally primarily as metabolites and 16%–61% of the dose is excreted in the feces as parent drug (Atripla™ 2006).

Food effects

As no formal drug-food interaction studies have been conducted and also due to increased drug exposure to efavirenz and tenofovir when taken with a high fat meal, it is

recommended that the dose of Atripla™ be taken once daily on an empty stomach (Atripla™ 2006).

Special populations

Sex

The pharmacokinetics of emtricitabine and tenofovir are similar between males and females. The results of studies examining sex differences in the pharmacokinetics of efavirenz are not fully conclusive. Three investigations have shown no influence of sex on the concentrations of efavirenz, whereas other studies have demonstrated mean efavirenz concentrations or a decrease in clearance in females compared with males (Barrett et al 2002; Csajka et al 2003; Lamba et al 2003; Kappelhoff et al 2005). At this time, there are no recommendations to alter doses based on sex (Atripla™ 2006).

Race

Ethnicity does not appear to alter the pharmacokinetics of emtricitabine (Emtriva® 2006). Data regarding the effects of race or ethnicity on tenofovir pharmacokinetics are limited at this time (Viread® 2007). There are ethnic-related differences in the pharmacokinetics of efavirenz. These may be related to genetic diversity found in the primarily metabolizing enzyme of efavirenz, CYP450-2B6 (see section below), but ongoing research will hopefully provide definitive explanations (Gatanaga et al 2007). Nonetheless, higher plasma concentrations and lower clearance values for efavirenz have been observed in Hispanics and African ethnic groups as compared to non-Hispanic whites (Csajka et al 2003; Pfister et al 2003). Currently, there are no recommendations to alter dose based on race (Atripla™ 2006), but enhanced vigilance in these populations for efavirenz adverse effects is warranted.

Renal impairment

The pharmacokinetics of emtricitabine and tenofovir (given as tenofovir) are altered in renal impairment. Emtricitabine AUC values increased 2.1-fold [11.8 h*μg/mL (± 2.9) to 25.1 h*μg/mL (±5.7)] in patients with a creatinine clearance of ≥80 mL/min compared to those with creatinine clearance of 30–49 mL/min. (Emtriva® 2006) Tenofovir's AUC values mimicked this as well, increasing 2.75-fold [2184 h*μg/mL (±257) to 6008 h*μg/mL (± 2504)] given similar changes in renal function (Viread® 2007). As efavirenz does not require dose adjustment based on renal dysfunction, Atripla™ should not be administered to patients with a creatinine clearance of <50 mL/min (Atripla™ 2006). If these agents are to be administered, separate dosage forms would need to be employed.

Hepatic impairment

The pharmacokinetics of tenofovir is not substantially altered by the presence of hepatic impairment (Viread® 2007). Because it is not extensively metabolized and is primarily renally eliminated, emtricitabine disposition would not be expected to be significantly altered with hepatic impairment (although to date this has not been well studied) (Emtriva® 2006). Given efavirenz's extensive hepatic metabolism, the manufacturer warns against using Atripla™ in patients with hepatic liver functions that are greater than 5 times upper limit of normal (Atripla™ 2006). This must be taken in concert with current treatment guidelines that recognize that though the risk for adverse effects is increased in those with hepatic impairment, that efavirenz instead should be used "with caution" (Bartlett and Lane 2007).

Genetic influences on the pharmacokinetics

Host genetic polymorphisms in drug metabolizing enzymes may also influence drug concentrations, drug clearance and/or drug efficacy (Gatanaga et al 2007). Efavirenz is metabolized primarily by CYP2B6 (Ribaudo et al 2006). The gene that encodes for CYP2B6 is highly polymorphic and has numerous single nucleotide polymorphisms (SNP) and associated haplotypes (Haas et al 2004). One important 2B6 polymorphism is the 2B6 G516T SNP. One study has demonstrated that the 516TT genotype of CYP2B6 was associated with higher plasma efavirenz concentrations (up to 3 times higher AUC in the TT variant) and predicted central nervous system side effects at week 1 of therapy (Haas et al 2004). However, tolerance to the CNS adverse effects developed after the first week, despite maintained higher efavirenz drug exposure (Haas et al 2004). In addition, ethnic differences in the frequency of the polymorphism were found. The frequency of the 516TT variant was higher in African Americans (20%) and European Americans (3%).

Other investigators have demonstrated that the G516T SNP also dictates efavirenz plasma half-life after discontinuation of efavirenz therapy. Essentially those with the faster metabolizing capability (GG) are able to 'metabolize' their side effects away as compared to those with the TT alleles (Ribaudo et al 2006). This finding led authors to speculate that the mutation may alter the risk of the development of drug resistance in patients discontinuing efavirenz containing therapy (Ribaudo et al 2006). Others have demonstrated that response to efavirenz treatment is due to a complex phenotype that is influenced by multiple genes, of which the G516T polymorphism is only one component of the

haplotype (Motsinger et al 2006). Additional studies are needed to clarify the genetic influences on efavirenz pharmacokinetics in order to improve the ability to individualize therapy and provide enhanced treatment strategies for HIV infected persons (Gatanaga et al 2007).

Drug interactions

There are many pertinent drug interactions associated with the individual drug components of Atripla™. Briefly, Atripla™ should not be co-administered with the antifungal drug voriconazole because efavirenz significantly decreases plasma concentrations of voriconazole (Atripla™ 2006). It is also not recommended that benzodiazepines (midazolam and triazolam) or ergot derivatives be used concurrently with Atripla™ due to the potential for prolonged or increased sedation (benzodiazepines) or peripheral vasospasms/ischemia of peripheral tissues (ergot derivatives). This interaction involves efavirenz's inhibitory effect on CYP540-3A4 (Atripla™ 2006). A recommended website to use for checking antiretroviral's drug interactions is www.hiv-druginteractions.org. This comprehensive site provides timely and referenced material related to the multitude of complicated interactions.

Adverse events and toxicity

There has been only one publication to date regarding use of the actual approved product (Mathias et al 2007). In this study, a single dose of Atripla™ was compared to a single dose of the individual medications (efavirenz + emtricitabine + tenofovir DF) in 48 fasting, non-HIV infected volunteers for pharmacokinetic purposes (Mathias et al 2007). Mild and transient headaches and dizziness were the most common adverse event, occurring in 24% of the volunteers receiving Atripla™ compared with 29% of the volunteers receiving the agents as individual agents (not significantly different). It is noteworthy, however that there were two serious adverse events in this trial. both were spontaneous abortions in the first trimester of pregnancy (this is described in greater detail below).

To date, there have been no large controlled clinical trials to evaluate the safety and tolerability of Atripla™ administered as approved and what is found in the package insert provides extrapolated information from previous studies (Atripla™ 2006). The following are based on adverse event data collected from studies (GS-99-934 and GS-99-903) using all three agents either as two (Sustiva® + Truvada®) or three (Sustiva® + Emtriva® + Viread®) individual agents (Gallant et al 2006; Arribas et al 2007a). Even within these studies, as the combination product (Truvada®) became available, adverse events and efficacy were not reported by specific elements, thus the generalization is made that these would not be different were these given together or separately. Additionally, another large dataset of adverse events can be cautiously extrapolated from ACTG 5142 in that tenofovir + efavirenz were primarily used in the NNRTI + 2 NRTI arm of this study, although lamivudine (Epivir®, Glaxo-SmithKline, Research Triangle Park, NC, USA) was used as the third agent and not emtricitabine (Riddler et al 2006).

In study GS-99-934, 63% (n = 163/257) and 56% (n = 142/254) of the efavirenz + emtricitabine + tenofovir group were found to have clinical and laboratory adverse events, respectively (Gallant et al 2006). The most common clinical events (occurring in >5% of patients) were dizziness, nausea, diarrhea, fatigue, headache and rash in this report. In the ACTG conducted study, 18% and 32% of participants were found to have Grade 3 or 4 clinical or laboratory adverse events, respectively (Riddler et al 2006). The clinical events reported here were not delineated by study arm unfortunately. Table 1 displays the primary laboratory abnormalities from these reports. Importantly, both studies had ≤10% participants discontinue due to intolerance/toxicity. System specific information on adverse events can be found in sections below.

Pregnancy

Women who are pregnant or planning to become pregnant should not take Atripla®. Women of child-bearing potential should be advised to use appropriate methods of birth control. Efavirenz has a well-established pregnancy contraindication and carries this into Atripla™ as noted by receiving a "D" pregnancy category rating (Atripla™ 2006). Documentation of pregnancy status should be verified prior to initiating ATRIPLA in women with childbearing potential.

Efavirenz

Neurological/psychiatric

Nervous system adverse events usually appeared during the first or second day of drug administration and generally resolved within 2–4 weeks of treatment (Atripla™ 2006). These events appear to be intensified with the use of alcohol or recreational drugs. This time-period, when the patient is at greatest risk for neurological adverse events, may present the greatest risk for poor adherence (see Adherence section below).

Skin rash

Mild to moderate maculopapular skin rashes occurring within the first two weeks of therapy can be seen in up to 26% with severe reactions (Stevens-Johnson syndrome) occurring in

Table 1 Adverse events occurring in ≥1% of persons on Atripla™ containing elements (Gallant et al 2006; Riddler et al 2006)

	GS-99-934 (through 48 weeks) (used all three elements of Atripla®)	GS-99-903 (though 144 weeks) (lamivudine in place of emtricitabine)	ACTG 5142 (through 96 weeks) (lamivudine in place of emtricitabine, n = 85)
	N = 257	N = 296	N = 250 (all NRTI combinations)
Fasting cholesterol >240 mg/mL	15%	NR	NR
Creatine kinase M: >990 U/L and F: >845 U/L	7%	12%	NR
Serum amylase >175 U/L	7%	9%	NR
AST M: >180 U/L and F: >170 U/L	3%	5%	4% (>5x ULN)
ALT M: >215 U/L and F: >170 U/L	2%	4%	3% (>5x ULN)
Alkaline phosphatase >550 U/L	1%	NR	NR
Hemoglobin <8.0 mg/dL	0%	NR	NR
Hyperglycemia >250 mg/dL	1%	NR	NR
Hematuria >75 RBC/HPF	2%	6%	NR
Neutrophils	3%(<1000 mg/mm^3)	3%	5%(<750 mg/mm^3)
Fasting triglyceride >750 mg/dL	4%	3%	3%

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; RBC/HPF, red blood cells per high power field; NRTI, nucleoside reverse transcriptase inhibitor.

less than 1% of patients treated with efavirenz (Atripla™ 2006). The typical skin reactions generally tend to be mild, responsive to antihistamine and/or oral corticosteroid therapy and usually resolve within 30 days.

Hepatic

As noted in the pharmacokinetic section, efavirenz is primarily eliminated by the liver (Atripla™ 2006). Cases of lactic acidosis and severe hepatomegaly have been reported and may be more likely to occur in those with pre-existing hepatic disease, concomitant administration of NRTI or other hepatically metabolized agents.

Tenofovir/emtricitabine

Adverse reactions that occurred in at least 5% of patients receiving tenofovir/emtricitabine include: anxiety, arthralgia, increased cough, dyspepsia, fever, myalgia, pain, abdominal pain, back pain, paresthesia, peripheral neuropathy, pneumonia, rhinitis, rash, urticaria, allergic reactions.

Patients receiving emtricitabine have reported a higher incidence of skin discoloration especially on their palms and soles of their feet. This change in skin pigmentation is usually asympatomatic, but may not resolve or do so slowly with discontinuation (Emtriva® 2006).

A decrease in bone mineral density (BMD) has been reported in patients receiving tenofovir. After 144-weeks of administration, protocol defined decreases in BMD was seen in 28% of the tenofovir DF group vs 21% of the control group (GS-99-903) (Gallant et al 2006). A statistically greater decrease in BMD of the lumbar spine and hip occurred in the tenofovir + efavirenz + lamivudine arm ($p = 0.001$ and $p < 0.06$, respectively) (Gallant 2006). From a clinically relevant standpoint, these changes occurred by week 24–48 and stabilized by week 144 and all fractures on this arm of the study were related to trauma.

Lactic acidosis and severe hepatomegaly with steatosis have been reported with nucleoside analogs, such as emtricitabine and tenofovir albeit to an extent much less than seen with other drugs in this class (Abramowicz 2006a). Nonetheless, caution is warranted is used in patients with known risk factors for liver disesase. Though Atripla™ is not indicated for the treatment of chronic hepatitis B infection (HBV), both emtricitabine and tenofovir exhibit some activity against HBV (Emtriva® 2006; Viread® 2006). Importantly, 'flares' or exacerbations of HBV have been reported in patients upon discontinuation of emtricitabine and tenofovir (Bartlett and Lane 2007). Recent treatment guidelines recommend that in co-infected patients (HBV – HIV) fully suppressive antiretroviral regimens contain elements effective against HBV (tenofovir, emtricitabine or lamivudine) (Bartlett and Lane 2007).

Both tenofovir and emtricitabine undergo renal elimination, but only tenofovir (perhaps as a result of its active tubular efflux) has been associated with post-marketing reports

of renal toxicity (nephrogenic diabetes insipidus, Fanconi Syndrome, acute renal failure) and the most recent treatment guidelines list nephrotoxicity to potentially occur with its use (Karras et al 2003; Rollot et al 2003; Peyriere et al 2004; Ray et al 2006; Viread® 2006; Bartlett and Lane 2007). Despite a multitude of case reports appearing in the literature, it is important to reflect on the scientific rigor of case reports or series as compared to more formal comparisons using larger datasets – both prospective and retrospective, in treatment naïve and experienced patients, patients with normal and mild renal dysfunction, patients with and without diabetes mellitus, comparing women to men, which have assessed the renal toxicity of this agent (Izzedine et al 2004; 2005; Enejosa et al 2006; Gallant et al 2006; Staszewski et al 2006). Using this approach, the incidence of tenofovir-induced renal toxicity, based on current data is seemingly occurring at the same rate as the comparator agent(s) in each instance. Some have suggested assessing for an influence of tenofovir on renal function when a combination of abnormal plasma glucose and hypophosphoremia are present (Izzedine et al 2004).

Economic implications of Atripla™

When the combination product Atripla™ (efavirenz/emtricitabine/tenofovir) was released, it was slightly more expensive ($1,381) than purchasing the three components individually ($1,363) based on wholesale pricing (Abramowicz 2006a). If however, the patient had a copay in addition to the average wholesale price, Atripla™ would then cost the individual less (three co-pays vs one co-pay). From 2006 to 2007, the costs for all of these medications have increased. Based on current wholesale prices, Atripla™ is cheaper ($1,465 vs $1,479 per 30 days' supply) than if the three components are purchased individually (Fleming 2007). If the combination product, Truvada® (emtricitabine/tenofovir) is purchased and taken with efavirenz which provides the same combinations of medicines the cost is identical to purchasing Atripla™. Unless there are co-pays involved, there is no cost advantage of using Atripla™ over Truvada® plus efavirenz.

Atripla™ efficacy and place in therapy

Atripla™ is indicated for the treatment of HIV-1 infection in treatment naïve adults (Atripla™ 2006). Atripla™ is effective against HIV-1 infection alone, as a complete regimen, or in combination with other antiretroviral agents. All three antiretroviral agents have proven to be effective in the treatment of HIV-1 infection when combined appropriately (Abramowicz 2006b; Bartlett and Lane 2006; Hammer et al 2006; Bartlett and Lane 2007). There are multiple regimens for the initial treatment of HIV-1 infection in adults and many factors play a role in the selection of that initial regimen. The INITIO study compared the efficacy of two NRTI in combination with either a NNRTI, a PI or both. INITIO revealed that patients on the combination containing the NNRTI had achieved a higher rate of viral suppression with increased CD4 counts after 3 years of therapy when compared to the other two regimens (Frampton and Croom 2006). In part due to the INITIO study, many current HIV-1 initial treatment guidelines recommend the initial treatment of HIV-1 infection contain the non-nucleoside, efavirenz, combined with two NRTI (zidovudine or tenofovir plus lamivudine or emtricitabine) (Pozniak et al 2006; Bartlett and Lane 2007) GS-99-934 compared the elements contained in Atripla™ (drugs were individually administered and not available as a fixed-dose combination) versus fixed-dose Combivir® (zidovudine and lamivudine fixed dose twice daily) plus efavirenz in antiretroviral naïve patients. (Pozniak et al 2006). At week 48, 84% of subjects on the agents in Atripla™ had achieved a HIV RNA less than 400 c/mL compared to 73% of patients on the combivir/efavirenz regimen ($p < 0.05$). At week 96, 75% of subjects on the elements of Atripla™ had reached a HIV RNA less than 400 c/mL with 67% of subjects reaching a HIV RNA less than 50 c/mL compared to 62% of subjects on the Combivir/efavirenz regimen had reached a HIV RNA less than 400 c/mL with 61% reaching a HIV RNA less than 50 c/mL (statistically significant for the <400 measure only, $p = 0.004$). Thus, a consistent virologic response advantage to using the elements contained in Atripla™ was seen. Subjects on the elements of Atripla™ had an increase in their CD4 count of 270 from baseline, while subjects on the other regimen had a CD4 count increase of 237 from baseline at week 96 ($p = 0.036$). Ten of the subjects on the elements of Atripla™ developed resistance during the study while twenty patients on the combivir/efavirenz regimen developed resistance, primarily manifesting as resistance to lamivudine or emtricitabine (M184V) ($p = 0.036$). No patients' virus, when undergoing resistance testing after meeting protocol definition of virologic failure (consecutive viral loads of >400 copies/mL after previously responding) to the elements of Atripla™ developed a K65R mutation (signature resistance mutation for tenofovir) (McColl et al 2006; Pozniak et al 2006) GS-99-934 concluded that those subjects on the elements of Atripla™ had a significantly greater virologic suppression to HIV RNA less than 400 c/mL and a greater increase in CD4 cell count from baseline (Pozniak et al 2006).

GS-99-934 was the largest study conducted on the use of the elements of Atripla™ in treatment naïve subjects. Since this regimen worked well on treatment naïve subjects, questions were raised to its efficacy on treatment-experienced subjects. To evaluate the efficacy of Atripla™ in experienced patients, the COMET study was undertaken. COMET compared the effect of switching HIV-1 antiretroviral experienced subjects, who were stable on efavirenz, lamivudine, and zidovudine (not necessarily receiving Combivir®), to Atripla™. Those subjects that were switched to Atripla™ maintained viral suppression to less than 400 c/mL at week 24 and the proportion of patients with viral suppression to less than 50 copies increased significantly from 59% prior to the switch to 76% 24 weeks after the switch (Frampton and Croom 2006). These data may not necessarily support a difference in antiviral activity between the two regimens, but instead lend credence to long-standing principles of improved efficacy of medications through improvements in dosing and adherence.

One arm (n = 299) of the GS-99-903 study that was reported out to 144 weeks used 2 of the 3 elements of Atripla™, with the modification being lamivudine used in the place of emtricitabine (Gallant et al 2006). Briefly, the data from this study provides additional support that the combination of efavirenz with tenofovir (and in this instance lamivudine) represents an effective antiretroviral regimen with over 70% of participants achieving and maintaining virologic suppression (viral load <400 copies/mL) for this prolonged period. Further, immunologic response was mean increase in CD4 cells of 263 cells/μL and while neither immunologic or virologic responses were statistically different than the comparator arm, this demonstrates the staying power of these two elements of Atripla™.

Lastly, ACTG 5142 reported success using NNRTI based therapy in comparison to a 'boosted' PI anchored by lopinavir/ritonavir (Kaletra®, Abbott Laboratories, Abbott Park, ILL, USA) (Riddler et al 2006). As emtricitabine was not allowed as part of the NRTI backbone but instead lamivudine was used, a cautious and brief summary of this study is included. In this conference report, the NNRTI based regimen was superior to the PI based regimen as it pertains to time to virologic failure (p = 0.006), and a statistically significant difference was noted in percentage of participants with viral loads of <400 (p = 0.41) and <50 copies/mL (p = 0.003) when comparing the NNRTI based regimen to the PI based one (93% vs 86% and 89% vs 77%, respectively). Caution is recommended in considering this information as CD4 recovery was superior with the PI containing regimen (285 vs 241 cells/μL, p = 0.01) and may warrant greater consideration, dependent on the patient's needs.

Adherence

Lack of adherence to a medical regimen is a persistent problem for health care providers. Non-adherence for medications can range from 15% to 93%, with the average rate being 50% non-adherence for chronic health conditions (Haynes et al 1979; McDonald et al 2002; Rueda et al 2007). In HIV patients participating in an antiretroviral adherence study, only about 30% (n = 24/81) of patients showed acceptable (≥95% measured by MEMS caps) adherence to their therapeutic regimen (Paterson et al 2000). Providers strive to enhance adherence in HIV patients and view a 95% adherence rate to the treatment regimen as capable of producing the greatest treatment effect and diminishing the likelihood of resistant strains from developing (Vervoort et al 2006).

In individuals infected with HIV, lack of adherence to the medication regimen not only can increase the likelihood of negative outcomes for the individual patient, but can also lead to development and spread of multi-drug-resistant strains of the virus (Murri et al 2004). Failure to adhere to a medication regimen in HIV-infected individuals can thus result in disproportionate societal costs through transmission of drug-resistant strains to others.

Complex treatment regimens are commonly associated with poor compliance, and simplification of the regimen is among the most common recommendations to enhance adherence (van Dulmen et al 2007). Complexity in treatment has many components, including the number of pills that the patient must take, the number of daily doses and their timing, the requirement to take medications with/without meals, and the degree to which the regimen affects the patient's activities of daily living (van Dulmen et al 2007). Many HAART therapies are highly complex. Technical solutions, including automated reminders to take medications (eg, medication dispensers, electronic alerts), can improve adherence, but simplification is probably more effective overall.

Complexity in the medication regimen has ripple effects throughout the healthcare team. Clear instructions from providers are associated with improved adherence, but the ability of providers to give clear instructions about the medication regimen is compromised when the regimen is complex. Patients may experience lowered self-efficacy about their ability to adhere to a complex regimen over their lifetimes, and this can reduce their willingness to adhere to the regimen.

Because Atripla™ combines three different antiretroviral therapies into a single pill, compliance rates to this therapy

should be better than with more complex HAART. Atripla™ is taken once a day, and patients are encouraged to take it at night to minimize side effects, on an empty stomach. Theoretically, adherence rates to Atripla™ should be better than for the three individual antiretroviral therapies that make up Atripla™. Unfortunately, there are no data that speak to this hypothesis as current studies comparing the two regimens mandated equivalent adherence in order for subjects to remain on study.

A simpler regimen should lead to clearer instructions from providers about how to take the medication. Because Atripla™ should be taken before bed, the regimen should interfere less with a patient's activities of daily living and be easier to incorporate into a patient's daily activity pattern.

Patient-focused perspectives

Multiple patient-related factors as associated with reduced adherence in HIV patients. These include low patient self-efficacy, psychological distress and depression, forgetfulness, and inadequate confidence in treatment effectiveness (Vervoort et al 2006). Patient self-efficacy is the patient's belief in their own ability to perform the needed behaviors to adhere to the regimen. Theoretically, HIV-infected patients who believe they can successfully carry out the instructions given by their providers are more likely to adhere to the treatment program (Ammassari et al 2002). Because the recommended regimen for Atripla™ is very simple, the self-efficacy of patients to stay on the therapy should be enhanced.

Psychological distress, including depression, is a common correlate of many chronic disorders (Glaros and Glass 1993) and may also be associated with drug abuse. A few studies have suggested that treating depression enhances adherence to treatment in HIV patients (Sambamoorthi et al 2000; Turner et al 2003; Yun et al 2005; Chander et al 2006). Substituting Atripla™ for its individual components will not necessarily deal with psychological distress, and providers should remain alert to the presence of depression and other psychological disorders in their patients.

Forgetfulness can diminish adherence to treatment, and there are many sources of forgetfulness: AIDS-related dementia may lead to forgetfulness. Forgetfulness may be a mechanism to avoid having to deal with the everyday reality of HIV infection. Forgetfulness may occur because other demands on an individual's time may take priority over medication taking. Forgetfulness should be a diminished issue with Atripla™. The so-called "Premack principle" states that an effective way to reinforce or increase the frequency of a less frequent behavior (medication-taking) is to make access to another, more favored or more frequent behavior contingent on engaging in the less frequent behavior. In other words, a patient can be counseled not to go to bed (a frequent, preferred behavior) until they have taken their medication (the less frequent behavior). Except for patients whose lives are chaotic, connecting ingestion of an Atripla™ tablet with sleep should improve adherence and diminish the likelihood that "forgetfulness" in all its forms will affect medication-taking. Data are needed to determine if this hypothesis can be supported.

Conclusion

This article has provided a concise review of the available data on Atripla™. This agent appears to be a plausible regimen for most HIV infected populations without documented resistance to the agents contained within, with some exceptions (such as pregnancy potential, abnormal renal function) as noted above. Whether beginning in a naive patient or switching from other regimens for tolerability issues, Atripla™ represents a viable option. Its demonstrated advantages with respect to lipid and hematologic parameters and equivalent incidence of renal toxicity are tempered by the findings of bone mineral density decreases, however. Combining multiple mechanisms of action in a single dosing unit appears to improve efficacy, increase the likelihood for adherence and maintain viral suppression compared to administering these agents independently. It is suggested other pharmaceutical companies assess the potential to replicate this for the remaining antiretrovirals.

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