

Atripla™ – HIV therapy in one pill

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Abstract: In July 2006 Atripla™ was approved by the US Food and Drug Administration (FDA), combining the active ingredients of one NNRTI and two NRTIs. Atripla™ is the first “one-pill-daily” regimen licensed for the treatment of HIV-1 infection in patients older than 18 years. H was licensed in Europe in December 2007 Atripla™ contains efavirenz 600 mg, emtricitabine 200 mg, and tenofovir disoproxil fumarate 300 mg. It therefore combines 3 compounds which have been widely used before and which were recommended for initial therapy due to their potency, tolerability, and safety profile. Efficacy and safety data of efavirenz, tenofovir DF, and emtricitabine are reviewed and compared with other antiretroviral drugs, which are used as initial therapy for treatment-naïve patient.

Keywords: Atripla™ antiretroviral therapy, new “one-pill-daily” regimen, review efficacy and safety data

Background

It is almost 25 years since in 1983 the human immunodeficiency virus type I (HIV-1) was defined as the primary cause of the acquired immunodeficiency syndrome (Barré-Sinoussi et al 1983; Gallo et al 1984). Worldwide, the number of HIV-1 infected persons exceeds 33 million, the majority of whom live in the developing countries of Sub-Saharan Africa, Asia, and South America. With the introduction of protease inhibitors and non-nucleotide reverse transcriptase inhibitors to antiretroviral treatment regimens between 1995 and 1996, the so-called highly active antiretroviral therapy (HAART) was established resulting in a dramatic decrease in the mortality and morbidity of HIV infection. Nevertheless eradication of the virus still remains impossible. This implies that besides efficacy of antiretroviral therapy, health care providers have to focus on long-term toxicity, development of drug resistances, and tolerance by the patient, leading to an improved long-term adherence behavior. It has therefore been a goal of the pharmaceutical industry to reduce the daily pill-burden and to simplify antiretroviral therapy by developing a “one-pill-daily” regimen. To achieve this goal Bristol-Myers Squibb Co. and Gilead Sciences Inc. formed a joint venture, and in July 2006 Atripla™ was approved by the US Food and Drug Administration (FDA), combining the active ingredients of one non-nucleoside reverse transcriptase inhibitor, efavirenz, and two nucleoside reverse transcriptase inhibitors, tenofovir disoproxil fumarate (DF) and emtricitabine, all well-known substances. H was licensed in Europe in December 2007.

As of October 2007 there were 31 compounds and combinations formally approved by the FDA for the treatment of HIV infections. These compounds can be classified in 6 categories according to their point of intervention with the HIV replicative cycle: nucleoside reverse transcriptase inhibitors (NRTIs), nucleotide reverse transcriptase inhibitors (NtRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), fusion inhibitors (FIs), CCR5-chemokine receptor antagonists, and recently approved the integrase inhibitors.

While HAART originally consisted of a pill burden of 20–30 pills per day, this has been gradually diminished over the past few years. Fixed drug formulations combining 2 or 3 NRTIs, eg, Combivir®, Trizivir®, Kivexa®, or 2 PIs, eg, Kaletra®, became

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available and simplified therapy regimens. Nevertheless because most HIV-infected patients are likely to require prolonged and continuous antiretroviral therapy, there was a need for simpler, once-daily, well-tolerated regimens with minimal long-term toxicity and durable efficacy.

Current US and European guidelines favor backbone combination therapy consisting of 2 NRTIs plus either an NNRTI or a boosted PI (NIH 2007, EACS 2007). Tenofovir DF or zidovudine plus emtricitabine or lamivudine form the dual NRTI backbone in recommended NNRTI- or PI-based regimens. Except in women who currently are, or wish to become, pregnant efavirenz is the NNRTI of choice while ritonavir-boosted lopinavir (or low-dose ritonavir with atazanavir, saquinavir) are the PIs of choice.

The new "one-pill-daily" combination Atripla™ contains: efavirenz 600 mg, emtricitabine 200 mg, and tenofovir DF 300 mg. It therefore combines 3 compounds which have been widely used before and which were recommended for initial therapy because of its excellent potency, tolerability and favorable safety profile. We review relevant efficacy and safety data of efavirenz, tenofovir DF, and emtricitabine compared with other common alternative drugs, which are used as initial therapy in treatment-naive patient.

Efavirenz

Of all three compounds included in Atripla™, efavirenz has been available the longest and was the third NNRTI approved. The 006 Study in 1999 showed a superiority of efavirenz over indinavir (each given in combination with AZT + 3TC) (Staszewski et al 1999). Since then, efavirenz has been compared with other drugs in many large randomized studies. In general efavirenz showed better efficacy, as observed in the CLASS study, where efavirenz, used in combination with ABC + 3TC, was more effective than d4T or boosted amprenavir (Bartlett et al 2002). The ACTG 5095 study showed superiority of efavirenz over abacavir when used in combination with AZT + 3TC (Gulick et al 2004). The ACTG 384 trial showed a better efficacy of efavirenz compared with nelfinavir (Robbins et al 2003; Shafer et al 2003), whereas in AI424-034 efavirenz was not superior but at least comparable to atazanavir (Squires et al 2004). More recently the ACTG 5142 trial evaluated 3 different 2-class antiretroviral regimens in 753 treatment-naive patients: efavirenz + 2 NRTIs; lopinavir/ritonavir + 2 NRTIs; lopinavir/ritonavir plus efavirenz. ACTG 5142 could demonstrate the superiority of efavirenz to lopinavir/ritonavir in terms of time to virological failure and suppression of HIV RNA

to below 50 copies/mL. However, the efavirenz arm did not achieve quite as robust a CD4 count increase as the other two arms (Zuger 2006; Riddler et al 2006).

Efavirenz is well tolerated, but mild to moderate CNS side effects including dizziness and numbness are typical and appear relatively often in the first days to weeks of treatment. Although these symptoms seem to resolve during the course of treatment, mild effects may persist (Lochet et al 2003; Arendt et al 2007). It therefore has to be decided in each case if efavirenz should be replaced or if the patient is able to tolerate those symptoms. Another disadvantage should be mentioned: the rapid development of drug resistance when efavirenz is used as monotherapy or quasi-monotherapy due to failure of viral suppression by the backbone drugs. Once mutations like the point mutation at position 103 (K103N) occur, it indicates resistance towards all approved NNRTIs. Only the new NNRTI TMC 125, which is still in the approval process, seems to be unaffected by those mutations. One possible explanation for the rapid development of resistance mutations is the long half-life of NNRTIs (Muro et al 2005).

Tenofovir DF

Similar to nucleoside analogs which target the enzyme reverse transcriptase, tenofovir DF acts as a false building block. Unlike the nucleoside analogs, it is monophosphorylated and therefore referred to as a nucleotide analog. In the 902 and 907 studies, in which tenofovir was added to an existing HAART, the viral load fell by approximately 0.6 logs after 48 weeks (Schooley et al 2002; Squires et al 2003). Equivalent potency comparing tenofovir to d4T (with a backbone regimen of 3TC + efavirenz) in treatment-naive patients was shown in the 903 Study. Especially side effects such as polyneuropathy and lipid changes were significantly reduced when tenofovir was used. Investigator-reported lipodystrophy was less common in the tenofovir DF group compared with the stavudine group (9 [3%] of 299 vs 58 [19%] of 301, $p < 0.001$) (Gallant et al 2004). In 2001, the drug was approved and is now widely used in antiretroviral therapies. Several studies have recently shown an improvement of lipid profiles, serum lactate, and lipodystrophy in HIV-positive patients after switch to tenofovir (Llibre et al 2006; Claas et al 2007). The RAVE study, a randomized, open-label, comparative study of switching from a thymidine nucleoside analog to either tenofovir DF or abacavir in 105 individuals with clinically evident lipodystrophy, showed significant improvement in limb fat mass over 48 weeks in both groups. It should be mentioned that mean total cholesterol, low density lipoprotein cholesterol, and

triglycerides improved modestly with switching to tenofovir DF but were unchanged with abacavir (Moyle et al 2006).

However, in recent years conflicting data about the potential risk of nephrotoxicity associated with a mild to moderate disturbance of renal function, as well as several cases of renal failure, on tenofovir have been published. At the end of study 903 no significant differences in mean serum creatinine levels among 299 patients treated with tenofovir, efavirenz, and lamivudine and 303 patients treated with stavudine, efavirenz and lamivudine could be measured. Only 4 patients experienced a grade 1 creatinine elevation (>0.5 mg/dL from baseline) in the tenofovir DF group, compared with 2 patients in the stavudine group (difference ns) (Izzedine et al 2005). Nevertheless other studies found that patients treated with a tenofovir DF-containing regimen had a small but significantly greater decline in estimated creatinine clearance compared to individuals who received an alternative NRTI-containing regimen (-7.48 mL/min per 1.73 m² versus -0.87 mL/min per 1.73 m²; $p = 0.036$) (Julg et al 2005; Gallant et al 2005). Gilead Sciences Inc., the manufacturer of tenofovir, has since recommended that patients with renal disease require dosing interval adjustments (300 mg 3 times per week) when the creatinine clearance is less than 50 mL/min and avoidance of tenofovir when the glomerular filtration rate (GFR) is less than 30 mL/min. Nevertheless renal function in all patients on tenofovir-containing regimens should be monitored regularly.

Another concern with tenofovir was raised by the observation of Schmid and colleagues, who found a significant association between the use of tenofovir and the presence of the enzyme variant “macroenzyme creatine kinase type 2” (Macro CK2). Electrophoresis and immunoblotting demonstrated that the Macro CK2 in TDF-treated patients consisted of the ubiquitous mitochondrial creatine kinase (uMtCK) suggesting that the appearance of uMtCK in these patients might be a first indicator of mitochondrial toxicity of TDF in the kidney (Schmid et al 2006).

Study 903 at week 144 showed furthermore a significantly greater mean percentage decrease from baseline in bone mineral density (BMD) at the lumbar spine in patients receiving tenofovir + lamivudine + efavirenz ($-2.2\% \pm 3.9\%$) compared with patients receiving stavudine + lamivudine + efavirenz ($-1.0\% \pm 4.6\%$). In total, 28% of tenofovir-treated patients versus 21% of the stavudine-treated patients lost at least 5% of BMD at the spine or 7% of BMD at the hip.

One explanation could be an increased bone turnover, as a significant increases in biochemical markers of bone metabolism such as alkaline phosphatase, serum osteocalcin,

and serum C-telopeptide could be observed in the group on a tenofovir-containing regimen compared with the stavudine group (Gallant et al 2004).

In terms of drug resistance, which will be discussed later, the mutation K65R is selected by tenofovir and confers a 2- to 4-fold reduced susceptibility to this drug. However the incidence of K65R is low (3%) and has not been observed in clinical trials with the concomitant use of tenofovir and FTC.

Emtricitabine (FTC)

Another NRTI, FTC is a pyrimidine nucleoside analog. FTC is similar to lamivudine (3TC) but seems to be more effective in *in vivo* studies and has a longer half-life. Several phases 3 studies have demonstrated equal or superior activity of once-daily administration of FTC, when compared head-to-head with activity of stavudine and 3TC. In the FTC-301 study, FTC, didanosine, and efavirenz were compared with stavudine, didanosine, and efavirenz. Baseline characteristics were no different between the two groups. After 60 weeks, 76% of patients in the FTC arm had achieved and maintained HIV RNA loads of <50 copies/mL, compared with 54% in the stavudine arm ($p < 0.001$) (Saag et al 2004). Because renal excretion of unchanged drug is the principal route of FTC elimination, the potential of FTC to cause metabolic drug interactions is low. No specific drug interactions have been reported in the literature. Development of drug resistance to FTC is comparable to that observed with 3TC. Used as monotherapy, a single point mutation at position 184 of reverse transcriptase develops rapidly and confers cross-resistance to 3TC, but other nucleoside agents retain their activity (Sanne et al 2002; Rousseau et al 2003).

Truvada® (tenofovir DF/emtricitabine)

In 2005, a fixed-dose combination of FTC (200 mg) and tenofovir (300 mg) was licensed and has been widely used since. The combination of tenofovir + FTC (administered as separate tablets) plus efavirenz ($n = 258$ patients) was superior to zidovudine + 3TC (administered as a fixed-dose combination with combivir), and efavirenz ($n = 259$ patients) in study 934. Results at 48 week revealed that 84% of the tenofovir-FTC group achieved HIV RNA loads of <400 copies/mL, compared with 73% of the zidovudine-3TC group ($p = 0.002$) (Gallant et al 2006). Continued follow-up through week 96 demonstrated that patients treated in the tenofovir DF/emtricitabine arm continued to have higher rates of viral suppression (75%), versus patients in the zidovudine/lamivudine arm (62%) in maintaining HIV RNA levels <400 copies/mL (Pozniak et al 2006). Patients treated with

tenofovir DF/emtricitabine showed additionally greater gains in CD4 cell counts at week 96 (mean increase, 270 cells/mm³ versus 237 cells/mm³; $p = 0.036$, respectively).

Nevertheless a limitation should be mentioned, as a higher percentage of patients in the zidovudine-3TC group discontinued the therapy prematurely (9%) than in the tenofovir-FTC group (4%). Adverse events of grade 2–4 occurred in ~72% of both groups, and most commonly included nausea (7%–9%), dizziness (7%–8%), fatigue (8%), and diarrhea (5%–8%), but significantly more patients in the zidovudine/lamivudine group experienced a treatment-limiting toxicity (11% versus 5%; $p = 0.008$); anemia was the most common cause (14 versus 0 subjects in the emtricitabine/tenofovir DF group, $p < 0.001$).

Fourteen patients in the tenofovir DF/emtricitabine group versus 27 in the zidovudine/lamivudine group met the criteria for treatment failure in study 934 and had genotypic data for drug resistance available after 96 weeks of therapy (Pozniak et al 2006). Efavirenz resistance mutations were most common ($n = 10$), followed by the M184V/I mutation, for those patients who were receiving tenofovir DF/emtricitabine. It should be mentioned that M184 occurred at a lower rate in patients on tenofovir DF/emtricitabine compared with the zidovudine/lamivudine group. However, the feared K65R mutation did not arise in any patient, but study 903, which evaluated a combination of efavirenz and tenofovir DF with lamivudine instead of emtricitabine, 8 out of 299 (2.7%) patients developed the K65R (Margot et al 2006).

Atripla™

Atripla™ combines the individual strengths and weaknesses of these compounds. Of all combination therapies available at the moment, Atripla™ offers the most convenient dosing schedule and the fewest number of pills. The combination efavirenz/emtricitabine/tenofovir DF was in general much better tolerated and caused significantly less body fat change compared with the well-known mainstay zidovudine/lamivudine. In respect of these qualities, it seems to be more likely that patients will show a higher degree of adherence to this regimen compared with commonly available PI-based therapies. The concerns about the higher risk of missed doses in a once-daily regimen do not seem to be proven, but clinical results should be awaited.

Current international treatment guidelines recommend a fixed-dose dual-NRTI backbone of emtricitabine/tenofovir DF or zidovudine/lamivudine combined with either efavirenz or a boosted PI for initial therapy of treatment-naive patients. Choosing efavirenz as combination for the nuke backbone

in Atripla™ is supported by the ACTG 5142 study, which demonstrated superior efficacy and durability of an efavirenz-based regimen compared with a lopinavir-based combination. Choosing tenofovir DF/emtricitabine as the nuke backbone for efavirenz was supported by the 934 study, which showed that after 48 weeks, more patients treated with tenofovir DF/emtricitabine had viral suppression (84% versus 73%; $p = 0.002$) and fewer treatment-limiting toxicities (9% versus 4%) than the zidovudine/lamivudine arm (Galant 2006).

Finally, some side effects could be a limiting factor in using Atripla™. Tenofovir DF has shown a potential risk of nephrotoxicity although no association has been observed in clinical trials with long-term follow-up. Nevertheless multiple cases of acute renal failure and Fanconi's syndrome have been reported and several studies have shown a decrease in the estimated GFR. These cases occurred mainly in patients with pre-existing renal diseases. Therefore, patients should receive a baseline renal function evaluation prior to receiving Atripla™, and regular monitoring of renal function during the therapy. Those patients with estimated GFR < 50 mL/min should receive an alternative therapy.

As mentioned, efavirenz is teratogenic and should be avoided in pregnancy and carefully used in women of reproductive age. Additionally the use of Atripla™ in patients with pre-existing psychiatric disorders should be evaluated in each case, as conditions may exacerbate during therapy with efavirenz. Common mild CNS complaints under efavirenz are self-limiting in most patients but should be monitored and eventually the therapy must be switched.

In summary, Atripla™ represents the “one-pill-daily” version of a widely used antiretroviral drug combination, pooling potent efficacy with a beneficial tolerability and safety profile. Due to its unique dosing schedule it will be a first choice therapy in therapy naive patients. Drug interaction studies using the Atripla™ formulation remain to be conducted as well as directly comparative studies with other drug combinations.

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