An update on the use of Atripla® in the treatment of HIV in the United States

Michael A Horberg1
Daniel B Klein2

1HIV Interregional Initiative, Kaiser Permanente, Oakland, California, USA;
2Department of Infectious Diseases, Kaiser Permanente Hayward Medical Center, Hayward, California, USA

Abstract: Atripla® (Gilead Sciences Inc, Foster City, CA, USA and Bristol-Myers Squibb, New York City, NY, USA) is a coformulated single pill composed of efavirenz, emtricitabine, and tenofovir disoproxil, intended as a once-daily potent combination antiretroviral therapeutic agent. Its efficacy is equivalent to the 3 component drugs taken in a combination as single medications. The coformulated antiretroviral regimen can be quite effective in patients whose human immunodeficiency virus is sensitive to all 3 components of Atripla. However, women at risk of pregnancy, already pregnant, or nursing mothers should not take Atripla, due to the teratogenic potential of the efavirenz moiety. Adverse effects are similar to those seen with the constituent medications, including potential central nervous system effects and renal toxicity. Since its US Food and Drug administration approval, prescriptions for Atripla have increased steadily.

Keywords: tenofovir, efavirenz, emtricitabine, antiretroviral therapy

Introduction
Since the advent of highly active antiretroviral therapy (now referred to as combination antiretroviral therapy [CART]), high levels of adherence are requisite to achieve maximal viral control and to improve immunologic status, which results in fewer acquired immunodeficiency syndrome defining events and lower mortality.1,2 Adherence with greater than 90% of prescribed doses has been indicated to prevent development of resistance and to achieve maximal viral control. Such high levels of adherence require tremendous compliance to what have often been complicated medical regimens with many potential adverse effects.1–3 Many factors contribute to the likelihood of greater CART adherence, including patient’s belief in the efficacy of the regimen, lower pill burden, fewer or more manageable adverse effects, and less frequent dosing.4,5 Even going from twice-daily to once-daily regimens significantly improves adherence.4 Thus, the ongoing goals of CART regimen development have been lesser pill burden, fewer dosages during the day, and fewer adverse effects.4,7

Development of Atripla
The earlier CART regimens required multiple pills with multiple dosages during the day.9 These regimens usually consisted of more than 1 nucleoside reverse transcriptase inhibitor (NRTI) and a protease inhibitor (PI). By the late 1990s, the potent once-daily nonnucleoside reverse transcriptase inhibitor (NNRTI), efavirenz, was developed (200-mg tablet with therapeutic dose of 600 mg) and was used in combination with dual NRTI therapy then currently available, leading to twice-daily...
regimens with potentially no more than 5–6 pills/day. With the subsequent formulation of a 600-mg pill of efavirenz, the pill burden was then reduced by 2 pills.9 Many human immunodeficiency virus (HIV) clinical experts also desired PI-sparing regimens, believing that the non-PI regimens have fewer adverse effects.10,11 Tenofovir disoproxil fumarate (marketed as Viread®; Gilead Sciences Inc, Foster City, CA, USA) received United States Food and Drug Administration (US FDA) approval as a single 300-mg nucleotide reverse transcriptase inhibitor (NtRTI) pill taken once daily in October 2001.12,13 The antiretroviral medication soon became commercially available in combination with 200-mg emtricitabine (another NRTI) as single pill once-daily Truvada® (Gilead Sciences Inc, Foster City, CA, USA), further reducing pill burden and dosages during the day if combined with other once-daily medications.

Truvada plus efavirenz became a widely prescribed 2 pills once-daily regimen, especially among antiretroviral naive patients. All 3 medications were then coformulated into a single once-daily tablet called Atripla® (Gilead Sciences Inc, Foster City, CA, USA and Bristol-Myers Squibb, New York City, NY, USA) which was US FDA approved in July 2006, achieving the therapeutic goal of a single pill once-daily regimen.14 Of note, the coformulation required collaboration between 2 pharmaceutical corporations (Bristol-Myers Squibb and Gilead Sciences Inc), a novel development for the HIV pharmaceutical industry.

Pharmacokinetics
Atripla is available for oral administration and was found to be bioequivalent to the combination of the single drug preparations in an open-label crossover study of 48 healthy subjects.15 As a coformulated product, Cmax values with food, relative to the fasting state, were reduced for emtricitabine (29%), increased modestly (14%) for tenofovir, and increased greatly (39%–79%) for efavirenz with increased area under the curve (AUC) values for both tenofovir and efavirenz.14 The AUC values are relatively similar to the single drug levels for the individual medications when administered in combination. Due to the Cmax values with food, efavirenz is advised to be taken on an empty stomach (usually at bedtime), and the same recommendation applies to Atripla, in order to increase blood levels for emtricitabine and reduced for efavirenz.

Pharmacodynamics and efficacy
The mechanism of action of tenofovir and emtricitabine is based on the intracellular conversion of these drugs to their active metabolites, which then competitively inhibit HIV reverse transcriptase activity and viral replication.16,17 The mechanism of action of efavirenz is through noncompetitive inhibition of the HIV reverse transcriptase.16 Atripla is highly efficacious when appropriately prescribed.18,19 In the initial noninferiority clinical studies of the Atripla coformulation, not only was noninferiority demonstrated compared to the twice-daily efavirenz–Combivir® (zidovudine plus lamivudine as fixed drug combination; GlaxoSmithKline plc, Middlesex, England), but also superior efficacy was observed (71% HIV RNA < 400/mL with Atripla equivalent vs 58% with zidovudine-based regimen; P = 0.004).18 Fewer adverse effects also were reported, as well as improved adherence, compared with the Combivir-based regimen.18,19 The improved adherence to a single pill regimen is not surprising, given the earlier studies of CART adherence. In fact, the authors reported improved adherence and efficacy comparing Truvada–efavirenz with tenofovir plus lamivudine plus efavirenz (2 pills compared with 3 pills once daily).20 A systematic overview of efavirenz-based clinical trials found that Atripla (or tenofovir plus lamivudine with efavirenz) had greater virologic response and fewer discontinuations than that of other NRTI/NtRTI combinations with efavirenz.21

The CD4 cell count response for Atripla is similar to that of its constituent medications. However, initial studies indicated a better CD4 cell response with Atripla than Combivir plus efavirenz (190/μL vs 158/μL; P = 0.002).19 Other studies did not demonstrate a significant difference in CD4 changes between NRTI combinations together with efavirenz.22

Considerations with prescribing Atripla
As with any other CART regimen, a resistance test should be performed prior to regimen initiation.23,24 To prevent the development of resistance, the patient’s HIV virus should show susceptibility to all 3 components of the medication. The most common resistance mutations which would lead to decreased efficacy of Atripla are M184V/I (leading to emtricitabine resistance), K103N (efavirenz resistance), and K65R (tenofovir resistance).23,25 If any of these major mutations are present, Atripla should not be prescribed. The frequency of these mutations among antiretroviral naive patients vary based upon geographic location, but can be as high as over 17%.26 In the initial study of Atripla, the K103N was the most common resistance mutation which developed with its use,19 followed by the M184V mutation, but few patients developed the K65R mutation.16,19 These mutations likely impact the use of Atripla among antiretroviral-experienced
patients, as they are not unique to Atripla and can develop prior to Atripla use.27

Reverse transcriptase mutations are the most common mutations among antiretroviral-experienced patients; M184V/I and K103N are the 2 most common mutations, given the frequent previous use of lamivudine (very similar in structure and virologic behavior to emtricitabine) and NNRTI medications that share the K103N mutation leading to class resistance.28 However, these are not the only mutations that can lead to Atripla resistance and all resistance testing should be interpreted by a clinician well versed in HIV resistance mutations.23 Further, these resistance mutations also often preclude simplification of a PI-containing or more complex regimen in a virologic-controlled patient because these mutations may be “archived” by the virus and become manifest during incomplete antiretroviral therapy.

Resistance mutations are not the only prescribing consideration for Atripla. Tenofovir can be associated with decreased renal function, and patients with impaired renal function, including older patients with seemingly normal creatinine values or patients with early HIV-associated nephropathy, often require dose adjustment of tenofovir and emtricitabine or preclude the use of tenofovir.29,30 In these situations, the fixed milligram dosing of Atripla precludes its use. Further, efavirenz has been associated with its own adverse effects. If a patient has had a severe rash or Stevens-Johnson syndrome with another NNRTI, efavirenz should be avoided.31 Because of potential for neuropsychiatric side effects with efavirenz, there is still debate about the use of efavirenz among patients with severe psychiatric disorders.32,33

Another prescribing consideration for Atripla is pregnancy or the risk of pregnancy. Efavirenz is potentially teratogenic and should not be used in women of reproductive age who are not using effective contraception, nor during pregnancy as it is deemed US FDA class C.34 The contraindication also applies to breast-feeding mothers.35 Although tenofovir has not been completely studied for its use in pregnancy, it is not generally considered to be contraindicated during pregnancy. It should be noted that Atripla is formulated at adult dosages; it is not intended for pediatric patients.35

There is a unique patient profile for which Atripla may be ideally suited. HIV-infected patients with hepatitis B virus (HBV) coinfection likely benefit from the tenofovir–emtricitabine components of Atripla.36 Both tenofovir and emtricitabine have potent activity against hepatitis B. Patients with HIV/HBV coinfection have greater all-cause mortality and more aggressive liver disease.37 Therefore, they ideally should have viral suppression of both viruses.37 As with HIV disease, monotherapy (especially with lamivudine or emtricitabine) can lead to HBV resistance and disease progression.38,39 Truvada, whether as part of Atripla or prescribed as part of a different CART regimen, allows potent combination therapy against hepatitis B as well as serving as the dual NRTI agent for HIV treatment. However, efavirenz should be used with caution in patients with severe liver disease, and tenofovir has been associated with lactic acidosis and steatosis.16 As adefovir (approved in the United States at low doses for hepatitis B treatment) and tenofovir are similar medications, they should not be administered concurrently.16

### Adverse effects

In general, Atripla is well tolerated. The initial considerations of the adverse effects of Atripla relate to the constituent components of the medication. The adverse effects of efavirenz are likely to occur sooner than other adverse effects. Acute (within 6 weeks of efavirenz initiation) adverse effects are usually central nervous system related, such as sleep disturbance, neuropsychological complaints, such as poor concentration or mood change, or rash.33,40,41 The rash is usually a typical appearing drug-related generalized erythematous maculopapular rash. However, progression to Stevens-Johnson syndrome has been reported and severe rash requires discontinuation of the medication.33 Often, though, the rash responds to steroid treatment if started soon after onset and may not require medication discontinuation.

The sleep disturbances can be profound and can limit the use.33 However, the disturbances are thought to be self-limiting and most patients become used to the intense dreams. It should be noted that these central nervous system disturbances can occur even later in the course of treatment, and have been associated with poorer adherence and viral rebound.42 Although the neuropsychiatric effects of efavirenz can persist even through 2 years of therapy, studies have found them to be typically mild and tolerable.43 Long-term adverse metabolic effects, however, are not generally seen with efavirenz except hypertriglyceridemia (albeit less than with PI-containing regimens),44 but this effect can require treatment.45

The adverse effects of tenofovir are generally related to the renal effects of the medication. The renal adverse effects can be both acute and long term. Tenofovir has been associated with renal failure (43.3/100,000 person-years in expanded access and postmarketing safety databases) and renal tubular dysfunction (22.4/100,000 patient-years).46–48 Several case reports have described the development of proximal tubular
dysfunction in patients taking tenofovir.59-55 The Swiss Cohort Study originally found tenofovir associated with renal function decline,56 although other studies have not found increased incidence of renal dysfunction with tenofovir compared with other NRTIs.10,46,57,59 or felt the effect to be limited.59-63 Kaiser Permanente’s retrospective analysis64 (tenofovir-containing regimen [964 patients] or tenofovir-sparing regimens [683 patients]) found that tenofovir-exposed patients had a larger relative decline in glomerular filtration rate (GFR) through 104 weeks (−7.6 mL/min/1.73 m² relative to tenofovir-sparing regimens; P < 0.001); the degree of the difference varied by baseline GFR, with the greatest effect seen in those patients with GFR > 80 mL/min/1.73 m². Also from the Kaiser Permanente study, tenofovir-exposed patients had more frequent development of proximal tubular dysfunction over time (at 52 weeks: hazard ratio [HR] adjusted = 1.95, P = 0.01 and at 104 weeks: HR adjusted = 5.23, P = 0.0004), and had greater risk of medication discontinuation (HR adjusted = 1.21, P = 0.02) especially as renal function worsened, as compared with other NRTI combinations. Due to renal dysfunction, some patients may require tenofovir dose adjustment; if so, Atripla needs to be replaced with its individual components with appropriate dose reduction based on creatinine clearance. It should be noted that although studies have found that the decrease in renal function is greater if tenofovir is administered with PI, there is still significant reduction with efavirenz.55,64

Tenofovir is further associated with Fanconi Syndrome, a proximal renal tubular disorder characterized by leakage of protein, glucose, amino acids, phosphate, and bicarbonate in the urine.65 Profound hypophosphatemia requiring phosphate repletion or medication discontinuation has been described. In addition, bone density loss and osteomalacia with teofivir use have been described, but the exact incidence is debated.16,66

The incidence of these adverse effects has not been reported to increase with coformulation of these constituent medications compared with the medications administered singly. However, longer term monitoring of the adverse effects of these medications (especially renal and bone complications) may demonstrate different incidences by formulation.

**Use of Atripla in the United States**

Atripla has found widespread use among antiretroviral naive patients. It is a recommended regimen for antiretroviral naive patients commencing antiretroviral therapy in many HIV treatment guidelines, including US Department of Health and Human Services expert panel guidelines.21 Its convenience and generally good tolerability make it a popular choice for both clinicians and patients. In a recent review of antiretroviral use in the Swiss Cohort, Atripla was the most frequent regimen used (28%).40

Even prior to the availability of Atripla, efavirenz and tenofovir had increasing prescriptions and market share.67 Since its arrival in the United States market, Atripla has steadily become the initial regimen of choice for antiretroviral naive patients initiating CART. Over 30% of all HIV-infected patients on antiretroviral therapy in the United States use Atripla (personal communication). Pharmaceutical sales experts predict that Atripla will have the highest antiretroviral sales by 2013, even as other presently available single agents decline in sales.68 Kaiser Permanente can serve as an example. Since 2006, Kaiser Permanente, an integrated US health care system and the largest civilian integrated provider of HIV care in the United States, has dispensed over 56,000 Atripla prescriptions, and this represents nearly 7% of all antiretroviral prescriptions in Kaiser Permanente during that time period. In 2009, 11% of all antiretroviral prescriptions filled in Kaiser Permanente were for Atripla, representing over 4,500 patients. Atripla was priced in the United States to be the equivalent price as the total cost of the 3 component medications.

As previously noted, its use in the United States for antiretroviral-experienced patients is more limited. Some switch studies from more complex or PI-based regimens to Atripla have shown continued viral control and success, but these studies have been among patients on their first antiretroviral regimen with likely prior susceptibility to the 3 antiretroviral medications in Atripla.69 Further, many patients can be safely changed from other NRTI combinations plus efavirenz to Truvada plus efavirenz (or Atripla).18 Also, many patients who were treated with the components of Atripla can be changed to the single pill once-daily safely.

**Conclusion**

Atripla is a potent and effective single pill once-daily antiretroviral regimen that works well in patients whose virus is susceptible to the 3 constituent medications. However, further drug development and coformulations of other antiretroviral medications, particularly with a once-daily administration, are needed because some patients cannot tolerate or are resistant to Atripla. Given also that Atripla cannot be utilized during pregnancy or breastfeeding, alternative coformulations should be developed. In addition, monitoring for long-term effects is still needed for Atripla, a consideration for its use in resource limited setting. As always, further investigation is needed.
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Disclosure

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