HIV/AIDS - Research and Palliative Care

Dovepress
open access to scientific and medical research

Open Access Full Text Article

REVIEW

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

This article was published in the following Dove Press journal:
HIV/AIDS - Research and Palliative Care
17 June 2010
Number of times this article has been viewed

Michael A Horberg[1]
Daniel B Klein[2]

[1]HIV Interregional Initiative, Kaiser Permanente, Oakland, California, USA; [2]Department 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.[6] 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.[8] 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

Correspondence: Michael A Horberg
Kaiser Permanente, 2000 Broadway, Oakland,
CA 94612, USA
Tel +1 510-891-3779
Fax +1 510-891-2829
Email michael.horberg@kp.org

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, C_{max} 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 C_{max} 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.[16] 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.[31,33] 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.[49–55] 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[19,46,57–59] or felt the effect to be limited.[59–63] Kaiser Permanente's retrospective analysis[64] (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 m^2 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 m^2. 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 teofovir 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.[23] 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.

Acknowledgments

The authors thank Ambrose Carrejo for drug utilization data in this manuscript. The authors acknowledge that they previously have received research grants from Gilead Sciences Inc, Bristol-Myers Squibb, and Merck Pharmaceuticals (the manufacturers of Atripla and its constituent medications), but these entities had no influence on this manuscript and the authors assume full responsibility for the content and opinions presented.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Bangsberg DR, Charlebois ED, Grant RM, et al. High levels of adherence do not prevent accumulation of HIV drug resistance mutations. *AIDS*. 2003;17(13):1925–1932.
2. Paterson DL, Swindells S, Mohr J, et al. Adherence to protease inhibitor therapy and outcomes in patients with HIV infection. *Ann Intern Med*. 2000;133(1):21–30.
3. Bangsberg DR, Kroetz DL, Deeks SG. Adherence-resistance relationships to combination HIV antiretroviral therapy. *Curr HIV/AIDS Rep*. 2007;4(2):65–72.
4. Chesney M. Adherence to HAART regimens. *AIDS Patient Care STDS*. 2003;17(4):169–177.
5. Chesney MA. Factors affecting adherence to antiretroviral therapy. *Clin Infect Dis*. 2000;30 Suppl 2:S171–S176.
6. Flexner C, Tierney C, Gross R, et al. Comparison of once-daily versus twice-daily combination antiretroviral therapy in treatment-naive patients: results of AIDS Clinical Trials Group (ACTG) A5073, a 48-week randomized controlled trial. *Clin Infect Dis*. 1;50(7):1041–1052.
7. Simoni JM, Frick PA, Pantalone DW, Turner BJ. Antiretroviral adherence interventions: a review of current literature and ongoing studies. *Top HIV Med*. 2003;11(6):185–198.
8. Bartlett JA, DeMasi R, Quinn J, Moxham C, Rousseau F. Overview of the effectiveness of triple combination therapy in antiretroviral-naive HIV-1 infected adults. *AIDS*. 2001;15(11):1369–1377.
9. Staszewski S, Morales-Ramirez J, Tashima KT, et al. Efavirenz plus zidovudine and lamivudine, efavirenz plus indinavir, and indinavir plus zidovudine and lamivudine in the treatment of HIV-1 infection in adults. Study 006 Team. *N Engl J Med*. 1999;341(25):1865–1873.
10. Corales RB, Shrestha NK, Taege AJ, et al. Protease-sparing regimen in a real-life practice with naive patients: an equal opportunity approach? *HIV Clin Trials*. 2001;2(1):17–21.
11. Knechten H, Sturner KH, Hohn C, Braun P. Switch to efavirenz in a protease inhibitor-containing regimen. *HIV Clin Trials*. 2001;2(3):200–204.
12. US Food and Drug Administration. Antiretroviral drugs used in the treatment of HIV infection. 2010. Available from: http://www.fda.gov/forconsumers/byaudience/forpatientadvocates/hivandaidsactivities/ucm118915.htm Accessed Apr 1, 2010.
13. Dando TM, Wagstaff AJ. Emtricitabine/tenofovir disoproxil fumarate. *Drugs*. 2004;64(18):2075–2082; discussion 2083–2074.
14. Frampton JE, Croom KF. Efavirenz/emtricitabine/tenofovir disoproxil fumarate: triple combination tablet. *Drugs*. 2006;66(11):1501–1512; discussion 1513–1504.
15. Mathias AA, Hinkle J, Menning M, Hui J, Kaul S, Kearney BP. Bioequivalence of efavirenz/emtricitabine/tenofovir disoproxil fumarate single-tablet regimen. *J Acquir Immune Defic Syndr (1999)*. 2007;46(2):167–173.
16. Bristol-Myers Squibb and Gilead Sciences Inc. Atripla (efavirenz/emtricitabine/tenofovir disoproxil fumarate) Prescribing Information 2010.
17. Frampton JE, Perry CM. Emtricitabine: a review of its use in the management of HIV infection. *Drugs*. 2005;65(10):1427–1448.
18. Arribas JR, Pozniak AL, Gallant JE, et al. Tenofovir disoproxil fumarate, emtricitabine, and efavirenz compared with zidovudine/lamivudine and efavirenz in treatment-naive patients: 144-week analysis. *J Acquir Immune Defici Syndr (1999)*. 2008;47(1):74–78.
19. Gallant JE, DeJesus E, Arribas JR, et al. Tenofovir DF, emtricitabine, and efavirenz vs zidovudine, lamivudine, and efavirenz for HIV. *New Engl J Med*. 2006;354(3):251–260.
20. Horberg MTB, Towner W, Bersoff-Matcha S, et al. Two Versus Three Pill HAART – Does it Make a Difference? [Oral abstract 44]. 3rd IAPAC/NIMH Conference on HIV Treatment Adherence. Jersey City, NJ, 2008.
21. Bartlett JA, Chen SS, Quinn JB. Comparative efficacy of nucleoside/nucleotide reverse transcriptase inhibitors in combination with efavirenz: results of a systematic overview. *HIV Clin Trials*. 2007;8(4):221–226.
22. Sax PE, Tierney C, Collier AC, et al. Abacavir-lamivudine versus tenofovir-emtricitabine for initial HIV-1 therapy. *New Engl J Med*. 2009;361(23):2230–2240.
23. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. In: Department of Health and Human Services, editor. Department of Health and Human Services; 2009:1–161.
24. Aberg JA, Kaplan JE, Libman H, et al. Primary care guidelines for the management of persons infected with human immunodeficiency virus: 2009 update by the HIV medicine Association of the Infectious Diseases Society of America. *Clin Infect Dis*. 2009;49(5):651–681.
25. Johnson VA, Brun-Vezinet F, Clotet B, et al. Update of the drug resistance mutations in HIV-1: 2009 Dec. *Top HIV Med*. 2009;17(5):138–145.
26. Rhee SY, Kantor R, Katzenstein DA, et al. HIV-1 pol mutation frequency by subtype and treatment experience: extension of the HIVseq program to seven non-B subtypes. *AIDS*. 2006;20(5):643–651.
27. Manfredi R, Rizzo E, Calza L, Chiodo F. The use of efavirenz as a part of late rescue antiretroviral treatment. *HIV Clin Trials*. 2001;2(5):413–420.
28. Campo RE, Lichtenberger PN, Rosa I, et al. Differences in the frequency of resistance to antiretroviral drug classes among human immunodeficiency virus type 1 clinical isolates. *J Clin Microbiol*. 2003;41(7):3376–3378.
29. Buskin SE, Torno MS, Talkington DF, et al. Trends in nephropathy among HIV-infected patients. *J Natl Med Assoc*. 2009;101(12):1205–1213.
30. Gupta SK, Eustace JA, Winston JA, et al. Guidelines for the management of chronic kidney disease in HIV-infected patients: recommendations of the HIV Medicine Association of the Infectious Diseases Society of America. *Clin Infect Dis*. 2005;40(11):1559–1585.
31. Colebunders R, Vanwolleghem T, Meurrens P, Moerman F. Efavirenz-associated Stevens-Johnson syndrome. *Infection*. 2004;32(5):306–307.
32. Clifford DB, Evans S, Yang Y, et al. Impact of efavirenz on neuropsychological performance and symptoms in HIV-infected individuals. *Ann Int Med*. 2005;143(10):714–721.
33. Maggiolo F. Efavirenz: a decade of clinical experience in the treatment of HIV. *J Antimicrob Chemother*. 2009;64(5):910–928.
34. Mirochnick M, Capparelli E. Pharmacokinetics of antiretrovirals in pregnant women. *Clin Pharmacokinet*. 2004;43(15):1071–1087.
35. Shlay JC, Sharma S, Peng G, Gibert CL, Grunfeld C. The effect of individual antiretroviral drugs on body composition in HIV-infected persons initiating highly active antiretroviral therapy. *J Acquir Immune Defic Syndr (1999)*. 2009;51(3):298–304.
36. Matthews GV, Seaberg E, Dore GJ, et al. Combination HBV therapy is linked to greater HBV DNA suppression in a cohort of lamivudine-experienced HIV/HBV coinfected individuals. *AIDS*. 2009;23(13):1707–1715.
37. Nikolopoulos GK, Paraskevis D, Hatzitheodorou E, et al. Impact of hepatitis B virus infection on the progression of AIDS and mortality in HIV-infected individuals: a cohort study and meta-analysis. *Clin Infect Dis*. 2009;48(12):1763–1771.

38. Nunez M, Perez-Olmeda M, Diaz B, Rios P, Gonzalez-Lahoz J, Soriano V. Activity of tenofovir on hepatitis B virus replication in HIV-co-infected patients failing or partially responding to lamivudine. *AIDS (London, England)*. 2002;16(17):2352–2354.
39. van Bommel F, de Man RA, Wedemeyer H, et al. Long-term efficacy of tenofovir monotherapy for hepatitis B virus-monoinfected patients after failure of nucleoside/nucleotide analogues. *Hepatology (Baltimore, Md)*. 2010;51(1):73–80.
40. Elzi L, Marzolini C, Furrer H, et al. Treatment modification in human immunodeficiency virus-infected individuals starting combination antiretroviral therapy between 2005 and 2008. *Arch Intern Med*. 2010;170(1):57–65.
41. Perez-Molina JA. Safety and tolerance of efavirenz in different antiretroviral regimens: results from a national multicenter prospective study in 1,033 HIV-infected patients. *HIV Clin Trials*. 2002;3(4):279–286.
42. Zaccarelli M, Soldani F, Liuzzi G, et al. CNS side effects as main risk factor for efavirenz failure and transient HIV-RNA elevation [abstract 720]. 9th Conference on Retroviruses and Opportunistic Infections. Seattle, Washington, USA: Foundation for Retrovirology and Human Health, Alexandria, Virginia, USA; 2002.
43. Fumaz CR, Munoz-Moreno JA, Molto J, et al. Long-term neuropsychiatric disorders on efavirenz-based approaches: quality of life, psychologic issues, and adherence. *J Acquir Immune Defic Syndr (1999)*. 2005;38(5):560–565.
44. Shikuma CM, Yang Y, Glesby MJ, et al. Metabolic effects of protease inhibitor-sparing antiretroviral regimens given as initial treatment of HIV-1 infection (AIDS Clinical Trials Group Study A5095). *J Acquir Immune Defic Syndr*. 2007;44(5):540–550.
45. von Giesen HJ, Koller H, de Nocker D, Haslinger BA, Arendt G. Long-term safety and efficacy of NNRTI within the central nervous system. *HIV Clin Trials*. 2003;4(6):382–390.
46. Nelson MR, Katlama C, Montaner JS, et al. The safety of tenofovir disoproxil fumarate for the treatment of HIV infection in adults: the first 4 years. *AIDS*. 2007;21(10):1273–1281.
47. Perazella MA. Drug-induced renal failure: update on new medications and unique mechanisms of nephrotoxicity. *Am J Med Sci*. 2003;325(6):349–362.
48. Peyriere H, Reynes J, Rouanet I, et al. Renal tubular dysfunction associated with tenofovir therapy: report of 7 cases. *J Acquir Immune Defic Syndr*. 2004;35(3):269–273.
49. Callens S, De Roo A, Colebunders R. Fanconi-like syndrome and rhabdomyolysis in a person with HIV infection on highly active antiretroviral treatment including tenofovir. *J Infect*. 2003;47(3):262–263.
50. Earle KE, Seneviratne T, Shaker J, Shoback D. Fanconi's syndrome in HIV+ adults: report of three cases and literature review. *J Bone Miner Res*. 2004;19(5):714–721.
51. Gaspar G, Monereo A, Garcia-Reyne A, de Guzman M. Fanconi syndrome and acute renal failure in a patient treated with tenofovir: a call for caution. *AIDS*. 2004;18(2):351–352.
52. Malik A, Abraham P, Malik N. Acute renal failure and Fanconi syndrome in an AIDS patient on tenofovir treatment – case report and review of literature. *J Infect*. 2005;51(2):E61–E65.
53. Quimby D, Brito MO. Fanconi syndrome associated with use of tenofovir in HIV-infected patients: a case report and review of the literature. *AIDS Read*. 2005;15(7):357–364.
54. Verhelst D, Monge M, Meynard JL, et al. Fanconi syndrome and renal failure induced by tenofovir: a first case report. *Am J Kidney Dis*. 2002;40(6):1331–1333.
55. Goicoechea M, Liu S, Best B, et al. Greater tenofovir-associated renal function decline with protease inhibitor-based versus nonnucleoside reverse-transcriptase inhibitor-based therapy. *J Infect Dis*. 2008;197(1):102–108.
56. Fux CA, Simcock M, Wolbers M, et al. Tenofovir use is associated with a reduction in calculated glomerular filtration rates in the Swiss HIV Cohort Study. *Antivir Ther*. 2007;12(8):1165–1173.
57. Gallant JE, Staszewski S, Pozniak AL, et al. Efficacy and safety of tenofovir DF vs stavudine in combination therapy in antiretroviral-naive patients: a 3-year randomized trial. *JAMA*. 2004;292(2):191–201.
58. Jones R, Stebbing J, Nelson M, et al. Renal dysfunction with tenofovir disoproxil fumarate-containing highly active antiretroviral therapy regimens is not observed more frequently: a cohort and case-control study. *J Acquir Immune Defic Syndr*. 2004;37(4):1489–1495.
59. Izzedine H, Hulot JS, Vittecoq D, et al. Long-term renal safety of tenofovir disoproxil fumarate in antiretroviral-naive HIV-1-infected patients. Data from a double-blind randomized active-controlled multicentre study. *Nephrol Dial Transplant*. 2005;20(4):743–746.
60. Antoniou T, Raboud J, Chirhin S, et al. Incidence of and risk factors for tenofovir-induced nephrotoxicity: a retrospective cohort study. *HIV Med*. 2005;6(4):284–290.
61. Padilla S, Gutierrez F, Masia M, Canovas V, Orozco C. Low frequency of renal function impairment during one-year of therapy with tenofovir-containing regimens in the real-world: a case-control study. *AIDS Patient Care STDS*. 2005;19(7):421–424.
62. Young B, Buchacz K, Baker RK, et al. Renal function in tenofovir-exposed and tenofovir-unexposed patients receiving highly active antiretroviral therapy in the HIV outpatient study. *J Int Assoc Physicians AIDS Care (Chic Ill)*. 2007;6(3):178–187.
63. Gallant JE, Winston JA, DeJesus E, et al. The 3-year renal safety of a tenofovir disoproxil fumarate vs a thymidine analogue-containing regimen in antiretroviral-naive patients. *AIDS*. 2008;22(16):2155–2163.
64. Horberg M, Tang B, Towner W, et al. Impact of tenofovir on renal function in HIV-infected, antiretroviral-naive patients. *J Acquir Immune Defic Syndr (1999)*. 2010;53(1):62–69.
65. Gupta SK. Tenofovir-associated Fanconi syndrome: review of the FDA adverse event reporting system. *AIDS Patient Care STDS*. 2008;22(2):99–103.
66. Cassetti I, Madruga JV, Suleiman JM, et al. 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*. 2007;8(3):164–172.
67. Jimenez-Nacher I, Garcia B, Barreiro P, et al. Trends in the prescription of antiretroviral drugs and impact on plasma HIV-RNA measurements. *J Antimicrob Chemother*. 2008;62(4):816–822.
68. Innovaro Pharmalicensing. Sales of antiretroviral agents will drive substantial six percent annual growth in the HIV drug market through 2013. 2009. Available from: http://pharmalicensing.com/public/press/view/1244103588_4a2783a4c60b2/ Accessed Apr 1, 2010.
69. Dejesus E, Young B, Morales-Ramirez JO, et al. Simplification of antiretroviral therapy to a single-tablet regimen consisting of efavirenz, emtricitabine, and tenofovir disoproxil fumarate versus unmodified antiretroviral therapy in virologically suppressed HIV-1-infected patients. *J Acquir Immune Defic Syndr (1999)*. 2009;51(2):163–174.