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A Randomized, Double-Blind Comparison of Tenofovir Alafenamide Versus Tenofovir Disoproxil Fumarate, Each Coformulated With Elvitegravir, Cobicistat, and Emtricitabine for Initial HIV-1 Treatment: Week 96 Results

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Abstract: In 2 double-blinded Phase 3 trials, 1733 antiretroviral-naive participants were randomized to tenofovir alafenamide (TAF), a tenofovir prodrug versus tenofovir disoproxil fumarate (TDF), each coformulated with elvitegravir/cobicistat/emtricitabine (E/C/F). At 96 weeks, 86.6% in the TAF arm and 85.2% in the TDF arm had HIV-1 RNA <50 c/mL [difference 1.5%; (95% CI: −1.8% to 4.8%)]. With TAF, there are smaller declines in bone mineral density and more favorable changes in proteinuria, albuminuria, and tubular proteinuria, and no cases of proximal tubulopathy compared with 2 for TDF. These longer-term data support E/C/F/TAF as a safe, well-tolerated, and durable regimen for initial HIV-1 treatment.

Key Words: tenofovir alafenamide, integrase inhibitor, randomized controlled trial, HIV, bone mineral density, renal safety

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INTRODUCTION

Nucleoside and nucleotide reverse transcriptase inhibitors (NRTIs) have been included in all regimens recommended by each major HIV treatment guideline panel.[1–4] Although newer agents in this antiretroviral class are much better tolerated than the NRTIs used earlier in the epidemic,

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there remain concerns for the potential for longer-term toxicity of the current NRTIs.[5]

Tenofovir disoproxil fumarate (TDF) is a potent and generally well-tolerated nucleotide analog, which has been associated with an increased risk of nephrotoxicity[6–8] and greater reductions in bone mineral density (BMD)[9–11] compared with other NRTIs. As a prodrug, TDF is metabolized to tenofovir (TFV), which, in turn, is metabolized intracellularly to its active metabolite, TFV diphosphate (TFV-DP). Higher circulating plasma levels of TFV have been correlated with both renal and bone adverse effects of TDF.[12] Tenofovir alafenamide (TAF) is also an oral prodrug of TFV, but is much more stable in plasma as compared with TDF, allowing for a ten-fold lowering of dose. These characteristics result in a substantial reduction (90%) in circulating TFV exposure, while achieving an approximately 4-fold increase in intracellular levels of TFV-DP in peripheral blood mononuclear cells.[13]

GS-US-292-0104 and GS-US-292-0111 (ClinicalTrials.gov, numbers NCT01780506 and NCT01797445) are 2 large randomized, international, double-blind, placebo-controlled trials comparing initiation of HIV therapy with TAF versus TDF in those also receiving elvitegravir (EVG, E), cobicistat (C), and emtricitabine (FTC, F) in single-tablet formulations. After 48 weeks, high rates of suppression of viremia below 50 copies per milliliter were observed in both study arms (TAF, 92% and TDF, 90%) and TAF met the primary objective of noninferior efficacy compared with TDF, defined as the proportion of participants who had HIV-1 RNA <50 copies per milliliter using the US Food and Drug Administration (FDA) snapshot algorithm.[14] Moreover, those assigned TAF had significantly reduced bone demineralization in the lumbar spine and hip; and a significantly smaller mean change in serum creatinine; significantly lower rates of total proteinuria, albuminuria, and proximal tubular proteinuria compared with those assigned TDF. In contrast, those assigned TDF experienced greater declines in lipids compared with those on TAF, with lower total, low density lipoprotein (LDL), and high density lipoprotein (HDL) fractions, as expected given the known off-target lipid effect of TDF in HIV-infected and HIV-uninfected individuals.[15,16] These improvements in bone and renal endpoints as well as the lack of off-target lipid effect are presumably driven by markedly lower plasma levels of TFV. We now present the safety and efficacy data collected from participants in these trials during the second year of on-study follow-up.

METHODS

Study Design and Participants

The design and inclusion criteria of the trials have been previously described.[14] Briefly, antiretroviral-naive adults (aged ≥18 years) with HIV-1 RNA at least 1000 copies per milliliter, estimated glomerular filtration (creatinine clearance, Cockcroft–Gault) rate of at least 50 mL/min, and genotypic sensitivity to EVG, FTC, and TDF were randomized 1:1 to receive once daily administration of TAF 10 mg versus TDF 300 mg, both coformulated with EVG 150 mg, cobicistat 150 mg, and emtricitabine 200 mg (E/C/F) with a double-blind, double-dummy design. Randomization was stratified by HIV-1 RNA (≤100,000 copies per milliliter, >100,000 to ≤400,000 copies per milliliter, or >400,000 copies per milliliter), CD4 count (<50 cells per microliter, 50 to 199 cells per microliter, or ≥200 cells per microliter), and region (United States, or non-United States) at screening.

Randomized participants were seen at screening, baseline, and at weeks 2, 4, 8, 12, 16, 24, 36, 48, 60, 72, 84, and 96. Laboratory tests included hematological analysis, serum chemistry tests, fasting lipid parameters, CD4 counts, measures of renal function (estimated creatinine clearance by Cockcroft–Gault, urine protein to creatinine ratio, urine albumin to creatinine ratio, retinol-binding protein to creatinine ratio, β2-microglobulin to creatinine ratio, fractional excretion of uric acid, and fractional excretion of phosphate) (Covance Laboratories, Indianapolis, IN), and measurement of HIV RNA concentration (Roche TaqMan 2.0; Roche Diagnostics, Rotkreuz, Switzerland). Participants with confirmed virologic failure (2 consecutive viral load samples >50 c/mL) and an HIV RNA >400 c/mL at week 8 or later had the second, confirmatory, sample sent for resistance analysis by GeneSeq Integrase, PhenoSense GT, and PhenoSense Integrase (Monogram Biosciences, South San Francisco, CA). Dual energy x-ray absorptiometry of the hip and lumbar spine was conducted at baseline and weeks 24, 48, 72, and 96.

The studies were approved by the US FDA and by institutional review boards at all sites.

Statistical Analysis

Noninferiority of TAF compared with TDF when each were combined with E/C/F was assessed by examining the proportion of participants in each arm with plasma HIV-1 RNA less than 50 copies per milliliter at week 96 as defined by the US FDA snapshot algorithm. An inferiority margin of 12% was prespecified with a 2-sided 95% CI (alpha level was not adjusted). Adverse events were coded with the Medical Dictionary for Regulatory Activities (version 18.0). We used Fisher exact test to compare treatment differences for adverse events and Wilcoxon rank-sum test to compare treatment differences for continuous laboratory test results (SAS, version 9.2; SAS Institute, Cary, NC).

RESULTS

Of the 2175 participants screened for both studies, 1744 were randomized and 1733 received at least one dose of study drug: 866 received TAF and 867 received TDF (see Table S1, Supplemental Digital Content, http://links.lww.com/QAI/A785 for baseline characteristics). There were high rates of retention through week 96 (TAF 89% versus TDF 87%). Baseline characteristics, as previously reported, were similar between treatment groups; 15% were female and 25% identified themselves as Black or of African descent. The median (Q1, Q3) baseline HIV-1 RNA was 4.58 (4.14, 4.96) $\log_{10}$ copies per milliliter, 17.4% had >100,000 to ≤400,000 copies per milliliter, and 5.2% had >400,000 copies per milliliter. At baseline, 2.9% had a CD4 cell count <50 cells per microliter, 10.3% had 50 to <200 cells per microliter, and 31.5% had

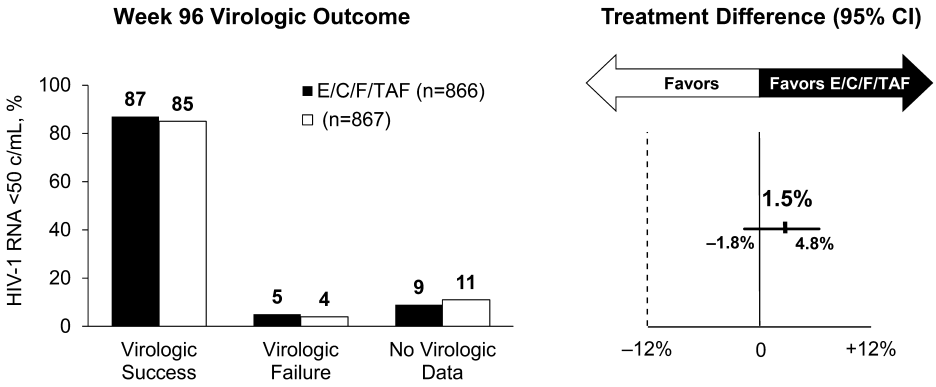

FIGURE 1. Viral Efficacy at Week 96 (FDA snapshot).

>500 cells per microliter. The median (Q1, Q3) values for estimated creatinine clearance (Cockcroft–Gault) at baseline were 115.6 mL/min (99.5, 134.4). Eleven percent of participants had a medical history of hyperlipidemia (n = 195).

At 96 weeks, 86.6% in the TAF arm and 85.2% in the TDF arm had HIV-1 RNA <50 c/mL (difference 1.5%; 95% CI [−1.8%, 4.8%]), (Fig. 1). By 96 weeks, virologic failure with resistance occurred in 18 participants: 10 of 866 (1.2%) in the TAF arm versus 8 of 867 (0.9%) participants in the TDF arm. In the TAF arm, detected resistance mutations included 6 participants with M184V/I plus EVG resistance mutations (T66A/I/V, E92Q, Q148R), 2 with only M184V/I, 1 with K65R plus M184V plus EVG resistance mutations (N155H), and 1 with K65N plus EVG resistance mutation (N155H). In the TDF arm, detected resistance mutations included 3 participants with M184V only, 2 with K65R plus M184V plus EVG resistance mutations (E92Q, Q148R), 1 with M184V plus EVG resistance mutation (E92Q), 1 with K65N plus EVG resistance mutation (N155H), and 1 with only EVG resistance mutation (N155S). For all of those with detected EVG resistance mutations, genotypic susceptibility to raltegravir was only retained for 3 of 18; genotypic susceptibility to dolutegravir was either retained or predicted to be retained by genotypic algorithm. Three participants in each arm had antiretroviral resistance that was newly detected between weeks 48 and 96. Across both arms, development of resistance was associated with higher baseline viral load. In the subjects with resistance, there was no statistical difference in baseline viral load between TAF and TDF arms (375,000 versus 105,000, respectively; $P = 0.2$).

Both regimens continued to be well-tolerated through week 96 with similar rates of drug-related adverse events in the TAF (42.4%) and TDF (45.9%) arms ($P = 0.15$). The most commonly reported drug-related adverse events in both arms were nausea, diarrhea, and headache—each occurring in less than 10% of participants. Adverse events leading to study drug discontinuation occurred in 10 (1.2%) on TAF versus 20 (2.3%) on TDF ($P = 0.096$) (see Table S2, Supplemental Digital Content, http://links.lww.com/QAI/A785 for details). Serious adverse events were infrequent and similar between groups (TAF, 11.2% versus TDF, 10.0%). Five (0.6%) participants in the TAF arm experienced serious adverse events that were considered drug-related by the investigator including abdominal pain, staphylococcal skin infection, rotator cuff syndrome, erythematous rash, and hypovolemic shock. In the TDF arm, 2 participants (0.2%) experienced serious adverse events that were considered drug-related by the investigator including cholelithiasis and immune reconstitution inflammatory syndrome. Likewise, grade 3 or 4 laboratory abnormalities were similar between the study groups (TAF, 27.6% versus TDF, 25.1%); the most common of these was elevation of creatine kinase (TAF, 9.4% versus TDF, 7.3%).

Participants receiving TAF had smaller declines in BMD at the hip and spine than those receiving TDF at week 48; the differences between the groups for both hip and spine BMD increased through week 96 (Fig. 2, Panel A). In the TAF group, hip BMD declined initially and then stabilized, whereas the TDF group continued to lose hip BMD. In the TAF group, spine BMD declined initially, stabilized, and trended toward improvement, whereas in the TDF group, spine BMD declined and stabilized. Fractures were rare in both treatment arms 3 (0.3%) in the TAF group and 9 (1.0%) in the TDF group ($P = 0.14$), and were reported to be due to trauma and unrelated to the study drug. After week 48, 3 male TDF participants (aged 20, 37, and 50) discontinued study medication because of a greater than 5% decrease in BMD as compared with no discontinuations due to BMD decreases in the TAF arm. Through 96 weeks, use of medications to improve bone density (mostly calcium and vitamin D supplementation) was reported by 15% of those in the TAF arm and 18% of those in the TDF arm ($P = 0.057$).

Through 96 weeks, the median change from baseline in estimated creatinine clearance was significantly lower with TAF than TDF (−2.0 mL/min versus −7.5 mL/min, respectively, $P \leq 0.001$). Significantly fewer participants in the TAF group (15.0%) had a ≥25% decrease from baseline in estimated creatinine clearance compared with the TDF group (30.2%) ($P \leq 0.001$). Quantitative markers of proteinuria (urine protein/Cr), albuminuria (UA/Cr) (Fig. 2, Panel B), and specific markers of proximal tubular proteinuria (retinol-binding protein/Cr and β-2-microglobulin/Cr) increased significantly in the TDF group, whereas significant declines or smaller increases were observed in the TAF group ($P < 0.001$ for all) (Fig. 2, Panel C). There were fewer participants in the TAF group with clinically significant proteinuria defined as UPCR >200 mg/g (n = 27 versus 42, $P = 0.030$) or clinically significant albuminuria (n = 37 versus 54, $P = 0.001$).

There were no discontinuations of study drug because of renal events in the TAF group, whereas there were 6

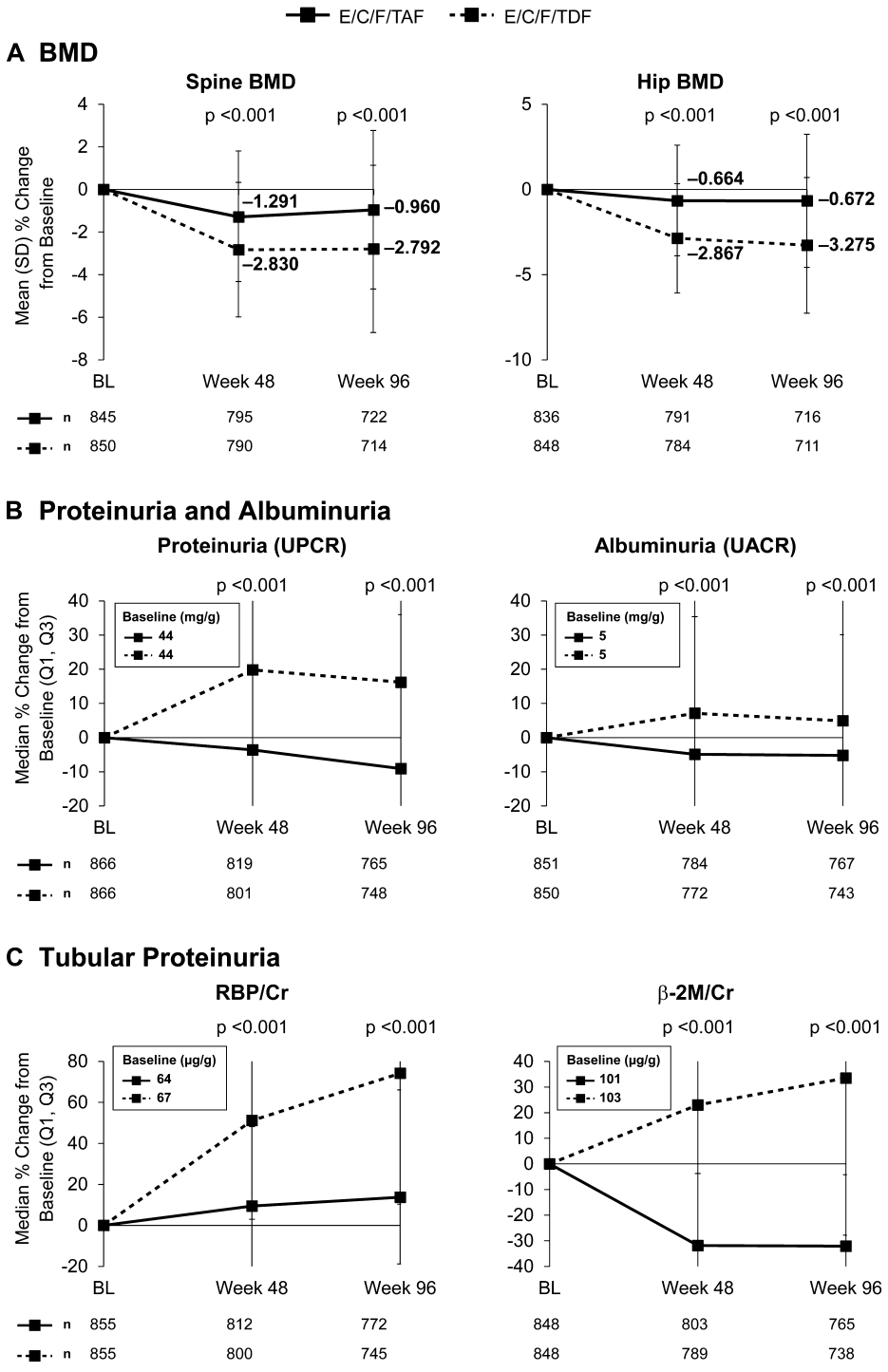

FIGURE 2. Week 96 Bone and Renal Outcomes. A, change in Spine and Hip Bone Mineral Density (BMD). B, change in Quantitativel Proteinuria. C, change in Tubular Proteinuria (RBP/Cr and β2-M/Cr).

participants who discontinued TDF because of renal adverse events ($P = 0.03$): 4 before week 48 and 2 after week 48 including one due to elevated creatinine and another due to proximal tubulopathy (reported by the site investigator as Fanconi syndrome/glycosuria). There have been no cases of proximal tubulopathy reported in the TAF group. In the TDF group, in addition to the discontinued participant noted above, another participant with tubular disorder has been reported and remains on study drug at the discretion of the site investigator.

Increases from baseline in total, LDL, and HDL cholesterol as well as triglycerides all were significantly greater in the TAF than TDF arm ($P < 0.001$ for all comparisons) (see Table S3, Supplemental Digital Content, http://links.lww.com/QAI/A785 for details). There were no differences between TAF and TDF in cardiovascular events:

2.4% versus 3.1% ($P = 0.46$), serious cardiovascular events: 0.6% versus 0.5% ($P = 0.75$), or rate of initiation of lipid-modifying agents: 3.8% versus 4.4% ($P = 0.63$).

DISCUSSION

After 2 years, the single-tablet regimen that combined TAF with E/C/F produced a rate of virologic suppression in treatment-naive participants that was high (87%) and remained noninferior to TDF. Concordant with this durably, high level of suppression of viral replication is the rare emergence of antiretroviral resistance in the 2 arms combined above, detected in only 1% (n = 18) of the 1733 participants.

During this extended period of study, both study regimens were well tolerated with few participants discontinuing therapy due to adverse events: 1.2% on TAF versus 2.3% on TDF. However, as seen at week 48, TAF continued to demonstrate a better bone and renal safety profile than TDF.[14] Despite a trend toward a greater use of agents to increase bone density in the TDF arm, the differences between TAF and TDF in BMD observed at week 48 widened by week 96, and spine BMD was observed to improve toward baseline levels during this period in those on TAF, while remaining decreased and largely unchanged in those on TDF. Similarly, markers of renal function persisted in being more favorable among those assigned to TAF. A small and rapid decline in estimated creatinine clearance is expected with administration of cobicistat, which is known to interfere with the tubular secretion of creatinine without affecting renal function. A characteristic decline in estimated creatinine clearance was observed in both study arms but was more profound in those in the TDF arm as demonstrated by the significant difference favoring TAF in the percent who had an estimated creatinine clearance decline of >25%. Tubulopathy, a rare toxicity of TDF, was reported in 2 participants receiving this agent, whereas it was not seen in any participant in the TAF arm. Together, these longer-term safety data support the hypothesis that circulating levels of TFV are responsible for the bone and renal toxicity of TDF and that the markedly reduced TFV level delivered by TAF minimizes such exposure and is protective against renal and bone effects.

Overall, in these large, international, randomized trials, at 96 weeks, 87% of those assigned to TAF combined with E/C/F were virologically suppressed; TAF remained noninferior to TDF in virologic efficacy and produced significantly more favorable changes in multiple markers of renal and bone health. These longer-term data support the use of TAF with E/C/F/as a safe, well-tolerated, and durable regimen for initial and ongoing HIV-1 treatment.

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REFERENCES

1. DHHS Panel on Antiretroviral Guidelines for Adults and Adolescents. *Guidelines for the Use of Antiretroviral Agents in HIV-1-infected Adults and Adolescents*. Department of Health and Human Services; 2011:1–166. Available at: http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf. Accessed September 28, 2015.
2. Thompson MA, Aberg JA, Hoy JF, et al. Antiretroviral treatment of adult HIV infection: 2012 recommendations of the international Antiviral Society–USA panel. *JAMA*. 2012;308:387–402. PMID: 22820792.
3. *European AIDS Clinical Society Guidelines for the Treatment of HIV (Version 7.1)*. Available at: http://www.eacsociety.org/guidelines/eacs-guidelines/eacs-guidelines.html. Accessed September 28, 2015.
4. *British HIV Association Guidelines for the Treatment of HIV-1-positive Adults with Antiretroviral Therapy*. 2012. http://www.bhiva.org/documents/Guidelines/Treatment/2012/hiv1029_2.pdf. Accessed September 28, 2015.
5. Solomon DA, Sax PE. Current state and limitations of daily oral therapy for treatment. *Curr Opin HIV AIDS*. 2015;10:219–225. PMID: 26049945.
6. Hall AM, Hendry BM, Nitsch D, et al. Tenofovir-associated kidney toxicity in HIV-infected patients: a review of the evidence. *Am J Kidney Dis*. 2011;57:773–780.
7. Gupta SK. Tenofovir-associated Fanconi syndrome: review of the FDA adverse event reporting system. *AIDS Patient Care STDS*. 2008;22:99–103.
8. Post FA, Moyle GJ, Stellbrink HJ, et al. Randomized comparison of renal effects, efficacy, and safety with once-daily abacavir/lamivudine versus tenofovir/emtricitabine, administered with efavirenz, in antiretroviral naive, HIV-1-infected adults: 48-week results from the ASSERT study. *J Acquir Immune Defic Syndr*. 2010;55:49–57.

9. Stellbrink HJ, Orkin C, Arribas JR, et al. Comparison of changes in bone density and turnover with abacavir–lamivudine versus tenofovir–emtricitabine in HIV-infected adults: 48-week results from the ASSERT study. *Clin Infect Dis.* 2010;51:963–972.
10. Schafer JJ, Manlangit K, Squires KE. Bone health and human immunodeficiency virus infection. *Pharmacotherapy*. 2013;33:665–682.
11. McComsey GA, Kitch D, Daar ES, et al. Bone mineral density and fractures in antiretroviral-naive persons randomized to receive abacavir-lamivudine or tenofovir disoproxil fumarate-emtricitabine along with efavirenz or atazanavir-ritonavir: Aids Clinical Trials Group A5224s, a substudy of ACTG A5202. *J Infect Dis.* 2011;203:1791–1801.
12. Van Rompay KK, Durand-Gasselin L, Brignolo LL, et al. Chronic administration of tenofovir to rhesus macaques from infancy through adulthood and pregnancy: summary of pharmacokinetics and biological and virological effects. *Antimicrob Agents Chemother*. 2008;52: 3144–3160.
13. Ruane PJ, DeJesus E, Berger D, et al. Antiviral activity, safety, and pharmacokinetics/pharmacodynamics of tenofovir alafenamide as 10-day monotherapy in HIV-1-positive adults. *J Acquir Immune Defic Syndr*. 2013;63:449–455.
14. Sax PE, Wohl D, Yin MT, et al; GS-US-292-0104/0111 Study Team. Tenofovir alafenamide versus tenofovir disoproxil fumarate, coformulated with elvitegravir, cobicistat, and emtricitabine, for initial treatment of HIV-1 infection: two randomised, double-blind, phase 3, non-inferiority trials. *Lancet*. 2015;385:2606–2615.
15. Tungsiripat M, Kitch D, Glesby MJ, et al. A pilot study to determine the impact on dyslipidemia of adding tenofovir to stable background antiretroviral therapy: ACTG 5206. *AIDS*. 2010;24: 1781–1784.
16. Mulligan K, Glidden DV, Anderson PL, et al. Decreases in cholesterol in HIV-seronegative men using emtricitabine/tenofovir pre-exposure prophylaxis: lipid results of iPrEx. Paper presented at: 15th International Workshop on Co-morbidities and Adverse Drug Reactions in HIV; October 15–17, 2013, Brussels, Belgium. http://www.intmedpress.com/serveFile.cfm?sUID=bc75b62c-c206-437a-b725-a75baa67f5b2. Accessed October 14, 2015.