A randomized, open-label, multicenter study was conducted to evaluate the therapeutic switch to a single-tablet formulation of efavirenz/emtricitabine/tenofovir DF (EFV/FTC/TDF) among virologically suppressed, HIV-1-infected subjects. Eligible subjects on stable antiretroviral therapy (ART) with HIV-1 RNA less than 200 copies per milliliter for 3 months or more were stratified by prior protease inhibitor (PI)- or non-nucleoside reverse transcriptase inhibitor (NNRTI)-based therapy and randomized (2:1) to EFV/FTC/TDF or to stay on their baseline regimen (SBR). Patient-reported measures were quality of life (QOL; SF-36 [version 2]), treatment adherence (visual analogue scale), preference of medication (POM), perceived ease of the regimen for condition (PERC), and a 20-item HIV symptom index. Overall, 203 subjects were randomized to EFV/FTC/TDF and 97 to SBR. Fifty-three percent of subjects had previously received a PI-based regimen; 47% an NNRTI-based therapy. Throughout the study, SF-36 summary scores did not differ significantly from baseline, regardless of previous ART or treatment allocation. Adherence was 96% or more in both groups at baseline and all subsequent study visits. At study conclusion, the EFV/FTC/TDF regimen was considered easier to follow than prior regimens by 97% and 96% of subjects previously receiving PI-based and NNRTI-based therapies, respectively. Overall, 91% of subjects switched to EFV/FTC/TDF indicated a preference over their prior therapy. Switching to EFV/FTC/TDF was associated with transient worsening/emergence of dizziness and sustained improvements in several other HIV-related symptoms. In conclusion, switching virologically suppressed, HIV-1-infected subjects from PI-based or NNRTI-based regimens to EFV/FTC/TDF was associated with maintained QOL and treatment adherence, and improved ease of use and treatment satisfaction.