

Bioequivalence of Efavirenz / Emtricitabine / Tenofovir DF Single Tablet Regimen

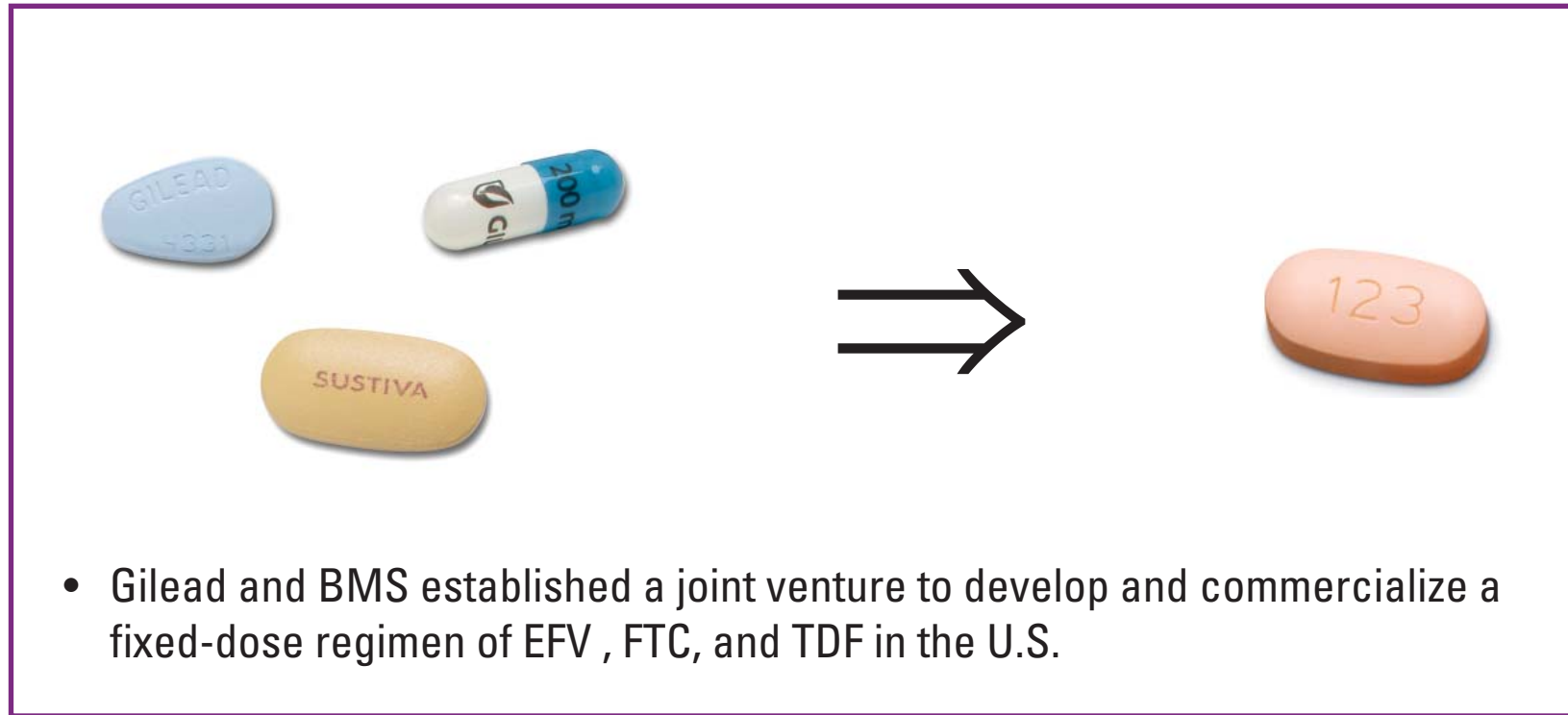
A Mathias, A Plummer, J Skillington, J Hui, J Hinkle, K Yale, and BP Kearney

Bristol Myers Squibb & Gilead Sciences LLC

Introduction

- Complex regimens may lead to poor adherence, development of drug-resistance and virologic failure
- Efavirenz (EFV), emtricitabine (FTC), and tenofovir DF (TDF) are preferred agents (DHHS, BHIVA, IAS, German-Austrian and French Guidelines) for the treatment of HIV-1 infection in appropriate patients
- To date there is no single tablet, once-daily, complete ARV regimen
- Potential benefits of a single tablet regimen
 - Simplify antiretroviral therapy
 - Improve patient compliance

Figure 1. EFV / FTC / TDF Single Tablet Regimen



Objectives

- To evaluate the pharmacokinetics and bioequivalence of a fixed-dose combination tablet
 - 600 mg EFV / 200 mg FTC / 300 mg TDF
 - Compared to commercial EFV + FTC + TDF
- To assess the safety of EFV, FTC, and TDF administered as single tablet regimen and as individual dosage forms

Results

Demographics

- 48 healthy subjects enrolled and 45 subjects completed the study
 - 35 female, 13 male
 - Hispanics 90%, Caucasian 6%, others 4%
 - Mean ± SD (range) age: 30 ± 7 yr (18 yr to 45 yr)
 - Mean ± SD (range) weight: 65.2 ± 7.15 kg (45.7kg to 81.1 kg)

Figure 3. EFV Plasma Concentration - Time Profile

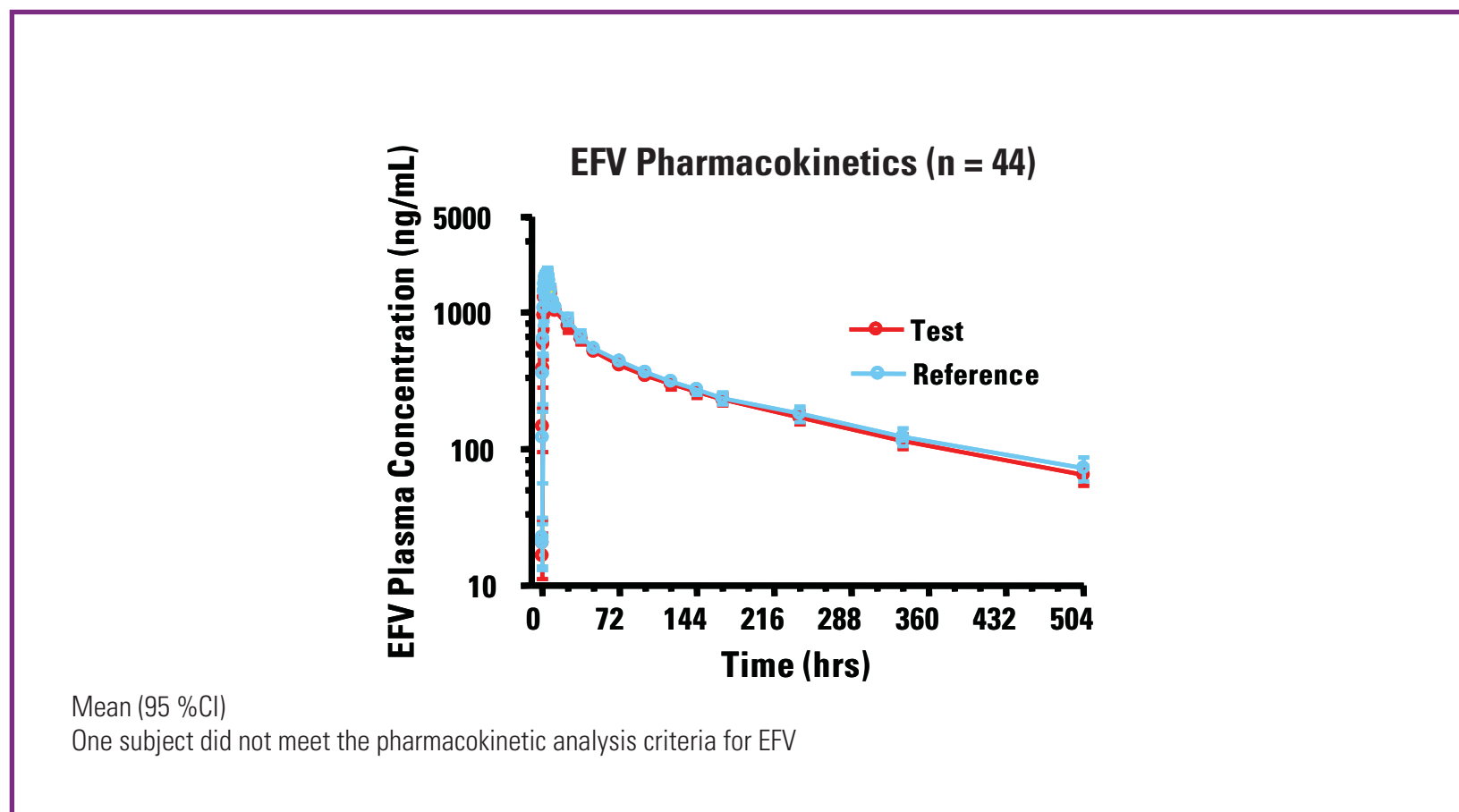
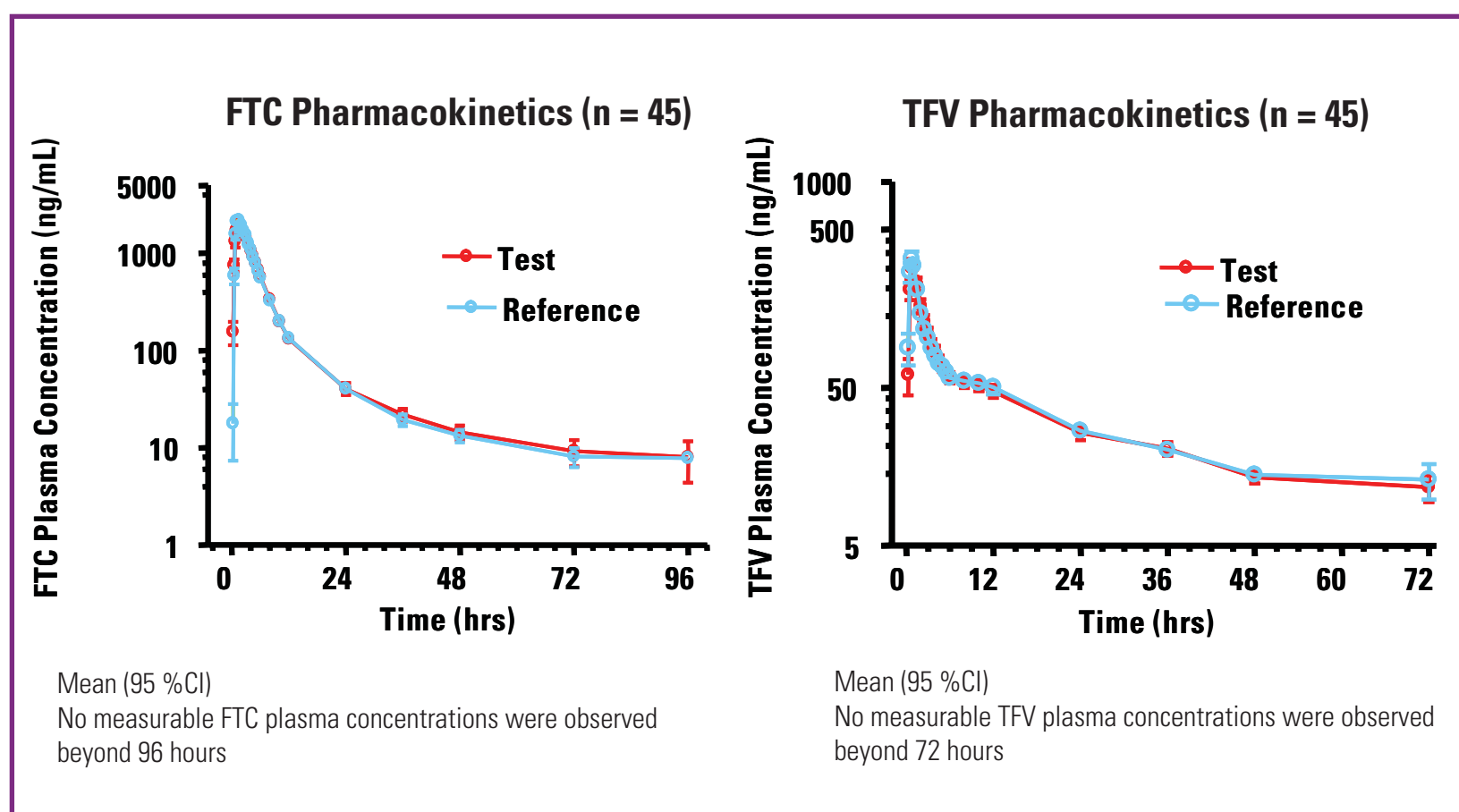


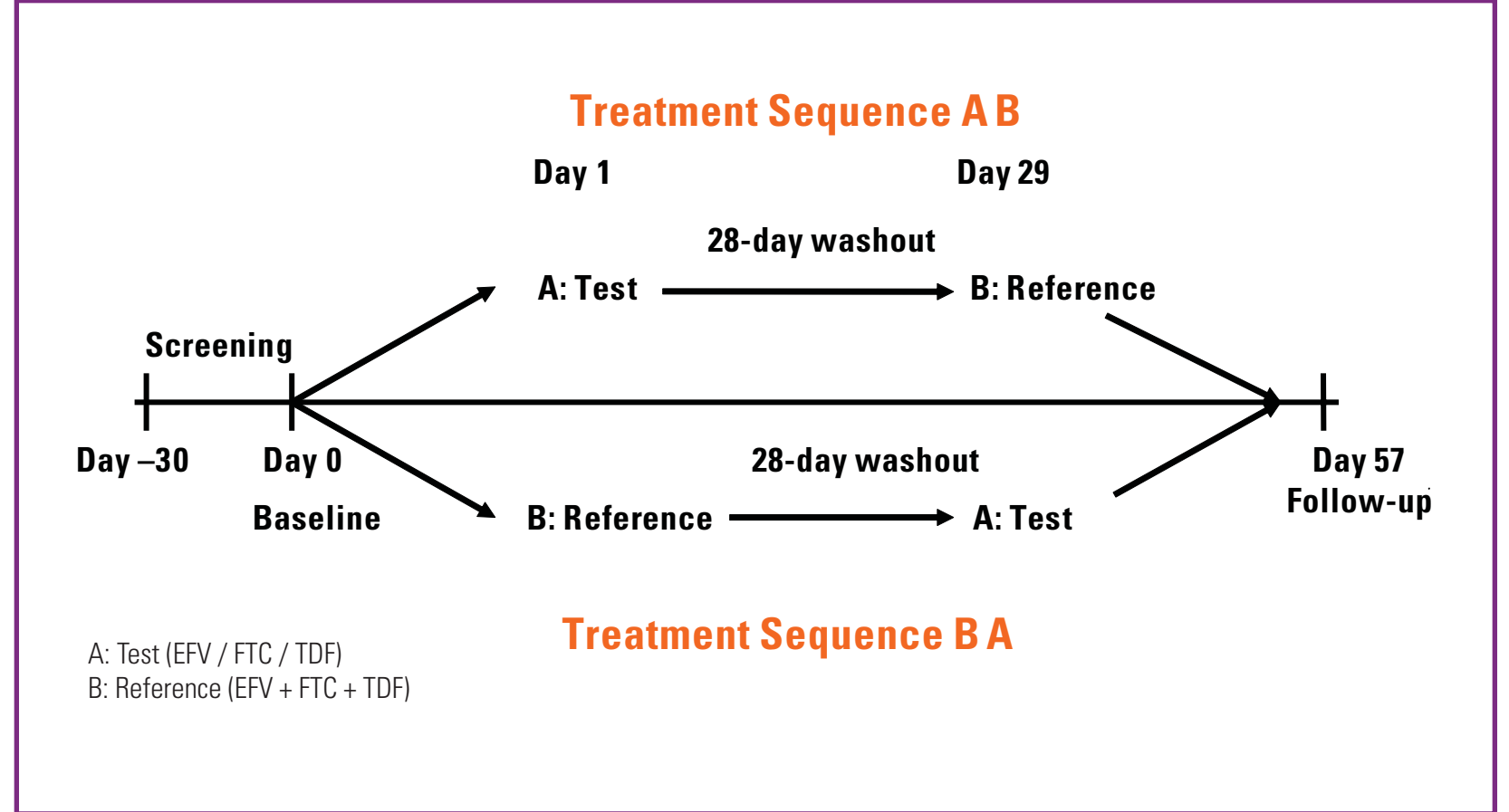
Figure 4. FTC Plasma Concentration and TFV Plasma Concentration - Time Profile



Methods

- A randomized, single-dose, open-label, two-way crossover in healthy subjects
- Fasted administration to test formulation performance

Figure 2. PK Study Design



- Pharmacokinetic Sampling
 - 21 days (504 hours)
 - Additional 7 day wash out due to long EFV half-life
- EFV, FTC and tenofovir (TFV) in plasma measured by LC/MS/MS
- Descriptive statistics and 90% CI for geometric mean ratios (GMR; Test vs. Reference) for EFV, FTC, and TFV C_{max} , AUC_{0-t} , and $AUC_{0-\infty}$ calculated using ANOVA
- Formulation bioequivalence concluded if 90% CI for the GMR for EFV, FTC and TFV C_{max} , AUC_{0-t} , and $AUC_{0-\infty}$ contained within 80% – 125%
- Safety was evaluated by physical examination, adverse events (AE) and laboratory assessments
 - Female subjects of childbearing potential were instructed to utilize highly effective contraception methods (2 separate forms of contraception) while on study and for 2 months following the last dose of study drugs

Table 1. Pharmacokinetic Parameters of EFV (n = 44)

PK Parameters	Test (EFV / FTC / TDF)	Reference (EFV + FTC + TDF)	% GMR (90% CI)
C_{max} (µg/mL)	2.28 (26.7)	2.30 (30.6)	99.9 (93.4, 107)
AUC_{0-t} (µg-hr/mL)	125 (25.9)	133 (27.3)	95.7 (90.5, 101)
$AUC_{0-\infty}$ (µg-hr/mL)	144 (32.0)	155 (35.1)	95.2 (88.9, 102)
$T_{1/2}$ (hr) ^a	164 (58.8, 533)	166 (43.0, 381)	-

Data presented as arithmetic mean (%CV) and as three significant figures
a. Median (min, max)

Table 2. Pharmacokinetic Parameters of FTC (n = 45)

PK Parameter	Test (EFV / FTC / TDF)	Reference (EFV + FTC + TDF)	% GMR (90% CI)
C_{max} (µg/mL)	2.13 (25.3)	2.38 (20.4)	88.8 (84.0, 93.9)
AUC_{0-t} (µg-hr/mL)	10.7 (18.1)	10.9 (14.9)	98.0 (94.9, 101)
$AUC_{0-\infty}$ (µg-hr/mL)	10.9 (17.9)	11.1 (14.9)	98.0 (94.9, 101)
$T_{1/2}$ (hr) ^a	10.6 (5.90, 47.5)	11.4 (6.60, 38.1)	-

Data presented as arithmetic mean (%CV) and as three significant figures
a. Median (min, max)

Table 3. Pharmacokinetic Parameters of TFV (n = 45)

PK Parameter	Test (EFV / FTC / TDF)	Reference (EFV + FTC + TDF)	% GMR (90% CI)
C_{max} (µg/mL)	0.325 (34.2)	0.353 (29.6)	91.5 (84.6, 98.8)
AUC_{0-t} (µg-hr/mL)	1.95 (32.9)	1.97 (32.8)	99.3 (91.0, 108)
$AUC_{0-\infty}$ (µg-hr/mL)	2.31 (29.2)	2.32 (30.3)	100 (93.2, 108)
$T_{1/2}$ (hr) ^a	18.5 (7.70, 28.4)	17.2 (7.80, 31.4)	-

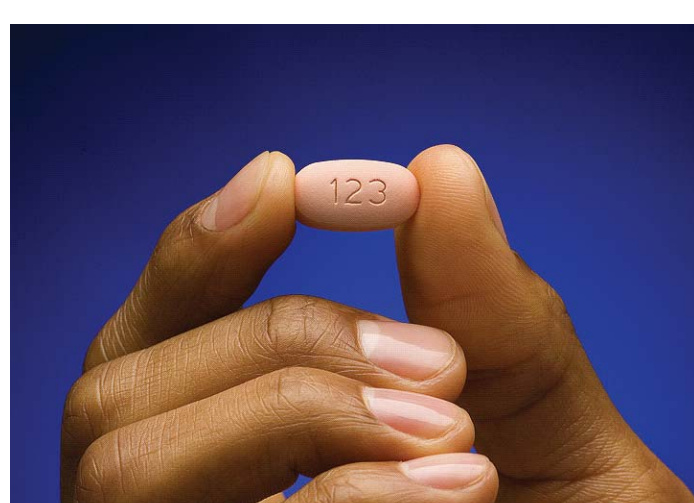
Data presented as arithmetic mean (%CV) and as three significant figures
a. Median (min, max)

- The 90% CI for the ratio of the geometric least-squares means of C_{max} , AUC_{0-t} and $AUC_{0-\infty}$ for the single tablet regimen versus the individual dosage forms were within 80% to 125% meeting the BE criteria for EFV, FTC and TFV

Safety Results

- EFV, FTC and TDF administered as EFV / FTC / TDF or as the individual dosage forms were generally well tolerated
- Two SAEs; spontaneous abortions in the first trimester in two subjects discontinued due to pregnancies
- One subject was discontinued due to a positive drug test
- CNS adverse events were the most frequent treatment-emergent, drug-related AEs
 - Primarily dizziness and headache
 - 24% of subjects with EFV / FTC / TDF
 - 29% of subjects with EFV + FTC + TDF
- Most AEs were mild, transient and consistent with known EFV, FTC, and TDF safety profiles

Conclusions



- A single tablet of EFV / FTC / TDF is bioequivalent to the individual EFV, FTC, and TDF dosage forms
- Represents the first once-daily single tablet regimen and contains 3 preferred ARVs for the treatment of HIV