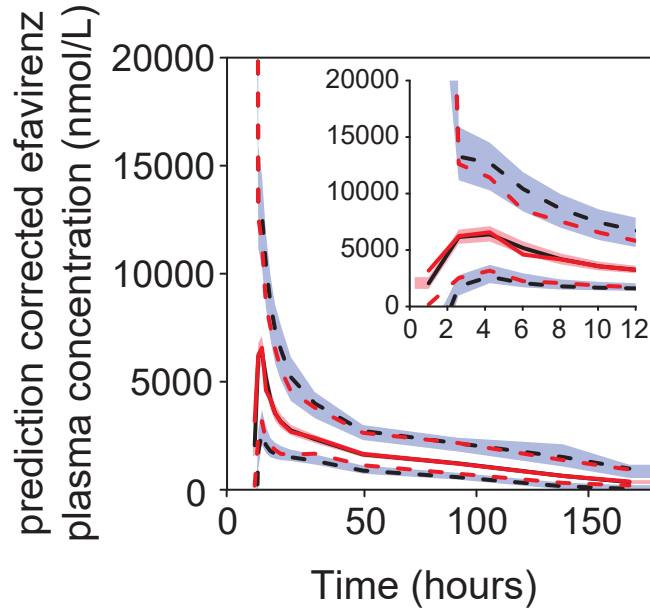


Supplemental Figure 1. Representative efavirenz plasma concentration profiles for subjects with empirically heterogeneous absorption kinetics. A: Slow initial absorption of variable duration, followed by a rapid absorption phase, resulting in differing T_{max} . B: Apparent mixed absorption kinetics resulting in a peaked C_{max} . C: Apparent mixed absorption kinetics resulting in plateaued, and poorly defined C_{max} . D: Rapid absorption with minimal apparent absorption lag time.



Supplemental Figure 2. Efavirenz plasma concentrations (prediction-corrected) and prediction-corrected visual predictive checks. The 95th, median, and 5th percentile of prediction-corrected efavirenz plasma concentrations (nmol/L) within each bin are represented by the upper red dashed line, middle red solid line, and lower red dashed line, respectively. The 95th, median, and 5th percentile of predicted plasma concentrations (nmol/L) within each bin are represented by the upper black dashed line, middle black solid line, and lower black dashed line, respectively. The red shaded area represents the 95% confidence interval for the median predictions, whereas the upper and lower blue shaded areas represent the 95% confidence intervals for the 95th and 5th percentile of predicted concentrations, respectively.

Supplemental Table 1. CYP450 Genotypes and Activity Classification

CYP450	Activity Classification	Star Allele Genotypes	Count	Frequency (%) *
CYP2B6	Normal	*1/*1, *1/*2, *1/*4, *1/*5	44	60.3
	Intermediate	*1/*6, *4/*9, *4/*6, *1/*18	23	31.5
	Slow	*6/*6	6	8.2
CYP2A6	Normal	*1/*1	56	78.9
	Intermediate	*1/*9	7	9.9
	Slow	*1/*2, *2/*2, *1/*12, *12/*12, *9/*9	8	11.3
	Missing	–	2	–
CYP3A4	Normal	*1/*1	67	94.4
	Intermediate	*1/*22	4	5.6
	Missing	–	2	–
CYP3A5	Normal	*1/*1	3	4.2
	Intermediate	*1/*3	15	21.1
	Slow	*3/*3, *3/*7, *7/*7	53	74.6
	Missing	–	2	–
CYP2C8	Normal	*1/*1	55	77.5
	Intermediate	*1/*2, *1/*3	15	21.1
	Slow	*2/*2	1	1.4
	Missing	–	2	–
CYP2C9	Normal	*1/*1	51	72.9
	Intermediate	*1/*2, *1/*3	12	17.1
	Slow	*2/*2, *2/*3, *3/*3	7	10.0
	Missing	–	3	–
CYP2C19	Ultra-rapid	*17/*17	4	5.5
	Normal	*1/*1, *1/*17	44	60.3
	Intermediate	*1/*2, *1/*2(*17), *2/*17, *1/*3	24	32.9
	Slow	*2/*2	1	1.4

* Frequency calculations exclude subjects with missing genotypes

Supplemental Table 2. Study Population Demographics and Anthropometric Measures
by Sex

	Female		Male		P-value *
	Median (Range)	Mean (SD)	Median (Range)	Mean (SD)	
Age (y)	22 (18, 47)	26.2 (8.4)	27 (18,50)	29.4 (10.4)	0.35
Weight (kg)	62.8 (53.1, 96.4)	65.9 (11.0)	76.6 (53.0, 103.6)	78.7 (12.3)	4.3e-05
Height (m)	1.68 (1.55, 1.81)	1.66 (0.07)	1.80 (1.65, 1.98)	1.79 (0.06)	4.5e-09
BMI (kg/m²)	23.0 (18.1, 32.2)	23.9 (4.3)	24.5 (17.8, 31.8)	24.4 (3.4)	0.30
Fat-free mass (kg)	41.6 (35.6, 53.7)	41.6 (4.4)	60.0 (46.7, 75.1)	60.8 (6.5)	3.0e-12
Fat mass (kg)	21.8 (16.5, 42.7)	24.3 (7.0)	18.0 (6.3, 32.7)	18.0 (6.3)	4.9e-04

* Two-sample Wilcoxon Rank Sum test

Supplemental Text: Comprehensive description of inclusion criteria, exclusion criteria and dietary restrictions

Study participation was dependent on subjects meeting the following criteria:

- 1) Male and female subjects between 18 and 49 years old.
- 2) HIV negative. All potential subjects will be HIV tested at screening visit.
- 3) Healthy individuals without any significant medical condition.
- 4) Adherence to the study dietary restrictions.
- 5) Nonsmoker or individuals willing to refrain from smoking or use of tobacco or marijuana for at least one month prior to and until the completion of the study. The entire study lasts for 30 days.
- 6) Ability to commit the time requested for this study.

Subjects were excluded from the study if they met one or more of the following criteria:

- 1) History or current HIV infection.
- 2) Life style that places you at a higher risk for contracting HIV (e.g. drug abuse, excessive alcohol drinking, and having multiple sexual partners).
- 3) Does not consent to HIV testing.
- 4) Underweight (weigh less than 52 kg or 114 lb) or overweight (body mass index (BMI) greater than 32).
- 5) History or current alcohol or drug abuse (more than 3 alcoholic drinks per day on a regular basis).
- 6) History of intolerance or allergic reaction (e.g. rash) to efavirenz, midazolam, tolbutamide, caffeine, or omeprazole.
- 7) History or current significant health conditions such as heart, liver, or kidney.
- 8) History or current psychiatric illness such as depression, anxiety, or nervousness.
- 9) History or current gastrointestinal disorders such as persistent diarrhea or malabsorption that would interfere with the absorption of orally administered drugs.
- 10) Individuals having a serious infection within the last month.
- 11) Donation of blood within the past two months.
- 12) Blood hemoglobin less than 12.0 mg/dl.
- 13) Individuals who are regularly taking prescriptions, over-the-counter, herbal or dietary supplements, alternative medications, or hormonal agents (i.e. oral contraceptives, intra-uterine device with hormones).
- 14) Females with a positive pregnancy test.
- 15) Breastfeeding.
- 16) Females of child-bearing potential who are unable or unwilling to either practice abstinence or use two non-hormonal forms of birth control (e.g. condom, contraceptive foams) up until the study completion, which will take a total of 30 days.
- 17) Participation in a research study or use of an investigational drug in the last two months.
- 18) An employee or student under supervision of any of the investigators of this study.
- 19) Individuals who cannot state a good understanding of this study including risks and requirements; are unable to follow the rules of this study.

Study subjects were asked to comply with the following dietary restrictions:

For at least 2 weeks prior to the start of the study and until study completion, volunteers will abstain from any prescriptions medications, over-the-counter medications, hormonal agents, herbal, dietary, and alternative supplements. For at least one week prior to the start of the study until completion, volunteers will not be allowed to eat any food or drink any beverages containing alcohol, grapefruit or grapefruit juice. Additionally, food or beverages items containing caffeine or xanthine (e.g. coffee, tea, chocolate, colas, Mountain Dew, etc.) must not be consumed 48 hours prior to beginning of the study day and during the 24 hours inpatient stays.