

A Steady-State Evaluation of the Potential Pharmacokinetic Interactions between Emtricitabine and Zidovudine in Healthy Volunteers

J Zong, M R Blum, G Chittick, R Hart, M Brosnan-Cook, and N Adda

Gilead Sciences, Inc., Durham, NC

Introduction

- Emtricitabine (Emtriva™, FTC), a newly approved NRTI, has shown potent and selective inhibition of HIV
- Zidovudine (Retrovir®, ZDV) is an approved NRTI for the treatment of HIV infection. It undergoes extensive hepatic metabolism to form inactive ZDV 5'-O-glucuronide (GZDV)
- Both FTC and ZDV/GZDV are eliminated primarily by active renal excretion. Since it is expected that FTC will be used in combination with ZDV, it is important to evaluate the potential pharmacokinetic (PK) interactions between these two drugs

Objective

- To determine the effect of zidovudine on the steady-state pharmacokinetics of emtricitabine
- To determine the effect of emtricitabine on the steady-state pharmacokinetics of zidovudine
- To evaluate the safety and tolerability of emtricitabine and zidovudine when administered alone and in combination for up to 7 days

Methods

- Randomized, open-label, 3-period crossover, steady-state drug-drug interaction study in 30 healthy male and female volunteers
- Eligible subjects were randomized to receive each of the following three 7-day treatments over a minimum 21-day treatment period (no washout):
 - Treatment A: 200 mg FTC QD x 7 days
 - Treatment B: 300 mg ZDV BID x 7 days
 - Treatment C: 200 mg FTC (QD) and 300 mg ZDV (BID) coadministered x 7 days
- Plasma concentrations of FTC and ZDV/GZDV were simultaneously analyzed by LC/MS/MS
- PK parameters were estimated by noncompartmental methods using WinNonlin™
- A conclusion of no clinically significant difference between the test (FTC+ZDV) and reference (FTC or ZDV) treatments was made if the 90% confidence intervals (CIs) of test/reference ratio for the geometric least-squares mean ratio for AUC_{ss}, C_{max} and C_{min} are each within the range of 0.7 and 1.43

Demographics

- 30 subjects enrolled: 13 female, 17 male
 - mean (range) age: 28 yr (19 to 44 yr)
 - mean (range) weight: 72.5 kg (62.2 to 92.6 kg)

Safety

- No serious adverse events were reported. Three subjects prematurely discontinued the study, two for AE (severe diarrhea and moderate nausea, respectively, both on zidovudine alone), and one who was unevaluable for the PK evaluation due to vomiting within 2 hours after dosing on PK days for successive treatment

Pharmacokinetics

Figure 1. Mean FTC Plasma Concentration vs. Time Profiles When FTC Administered Alone or in Combination with ZDV

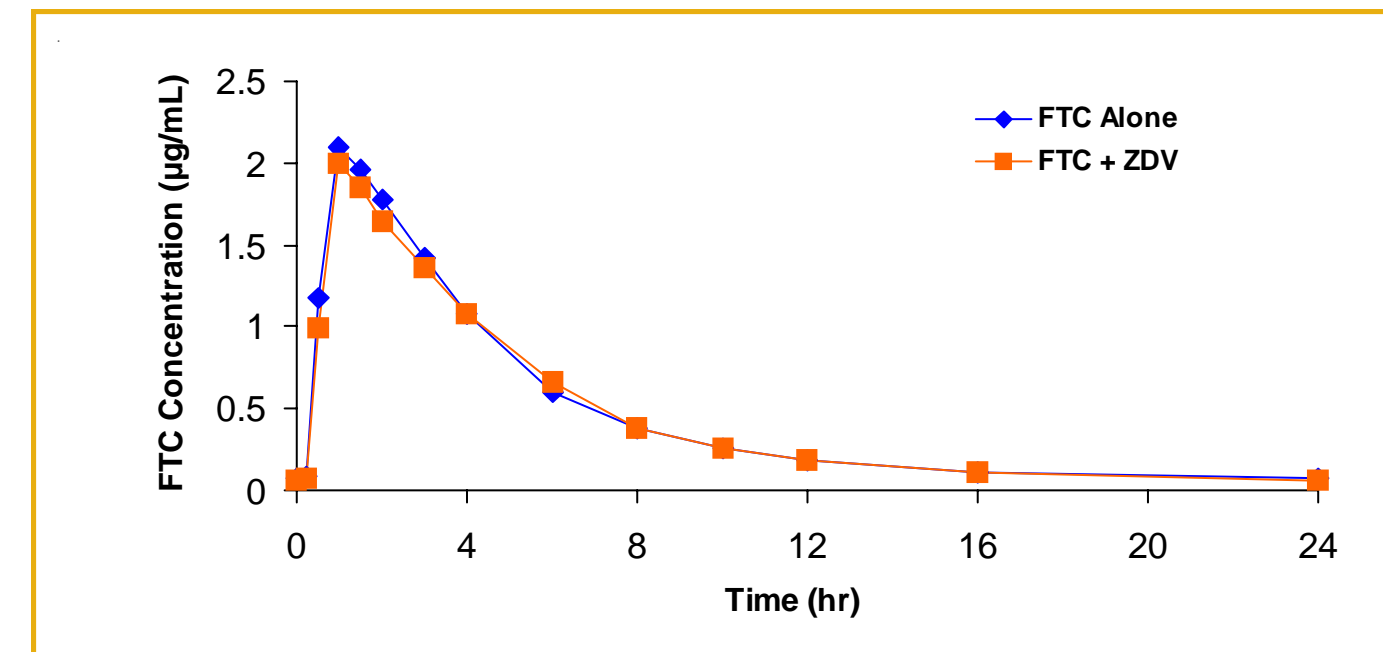


Table 1. Pharmacokinetic Parameter Estimates of FTC When FTC Administered Alone or in Combination with ZDV (N = 27)

PK Parameter ¹	FTC Alone	FTC + ZDV	Geometric Least Squares Mean Ratio (90% CI)
AUC _{ss} (µg·hr/mL)	10.7 (16)	10.4 (14)	0.97 (0.93 - 1.01)
C _{max} (µg/mL)	2.2 (21)	2.1 (20)	0.97 (0.90 - 1.04)
C _{min} (µg/mL)	0.07 (24)	0.07 (24)	0.96 (0.88 - 1.04)
t _{max} (hr)	1.2 (31)	1.2 (30)	N/A
t _{1/2} (hr)	9.4 (16)	9.3 (14)	N/A

¹ Mean (%CV)
PK parameters are presented as mean (%CV); AUC_{ss} = Steady-state AUC; C_{max} = Maximum plasma concentration; C_{min} = Minimum plasma concentration; t_{max} = Time to C_{max}; t_{1/2} = Terminal phase half-life

Results

Figure 2. Mean ZDV Plasma Concentration vs. Time Profiles When ZDV Administered Alone or in Combination with FTC

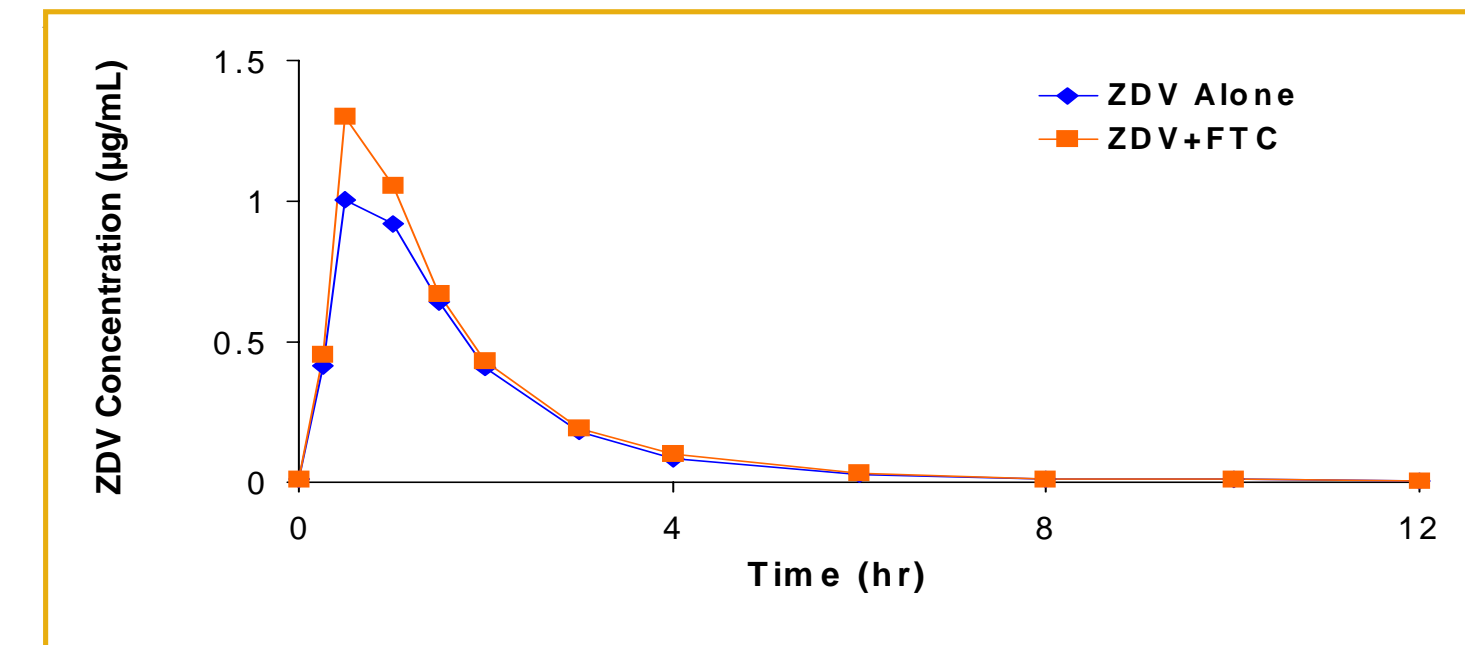


Table 2. Pharmacokinetic Parameter Estimates of ZDV When ZDV Administered Alone or in Combination with FTC (N = 27)

PK Parameter ¹	ZDV Alone	ZDV + FTC	Geometric Least Squares Mean Ratio (90% CI)
AUC _{ss} (µg·hr/mL)	2.0 (24)	2.2 (26)	1.13 (1.05 - 1.20)
C _{max} (µg/mL)	1.3 (42)	1.5 (40)	1.17 (1.00 - 1.38)
C _{min} (µg/mL)	0.005 (74)	0.004 (97)	0.98 (0.89 - 1.09)
t _{max} (hr)	0.8 (51)	0.7 (42)	N/A
t _{1/2} (hr)	3.0 (24)	2.8 (24)	N/A

¹ Mean (%CV)
PK parameters are presented as mean (%CV); AUC_{ss} = Steady-state AUC; C_{max} = Maximum plasma concentration; C_{min} = Minimum plasma concentration; t_{max} = Time to C_{max}; t_{1/2} = Terminal phase half-life

Figure 3. Mean GZDV Plasma Concentration vs. Time Profiles When ZDV Administered Alone or in Combination with FTC

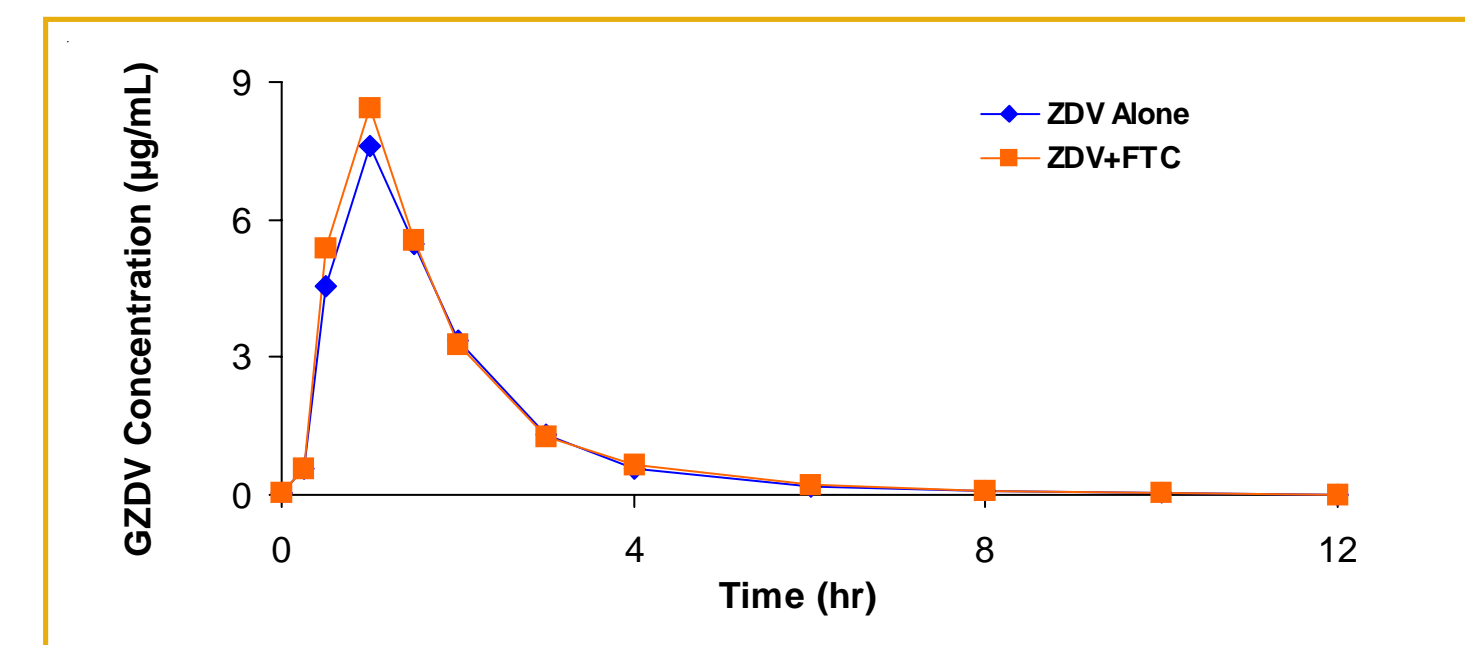


Table 3. Pharmacokinetic Parameter Estimates of GZDV When ZDV Administered Alone or in Combination with FTC (N = 27)

PK Parameter ¹	ZDV Alone	ZDV + FTC	Geometric Least Squares Mean Ratio (90% CI)
AUC _{ss} (µg·hr/mL)	13.2 (15)	14.1 (16)	1.06 (1.03 - 1.10)
C _{max} (µg/mL)	8.3 (20)	9.0 (18)	1.09 (1.01 - 1.18)
C _{min} (µg/mL)	0.02 (96)	0.02 (96)	0.87 (0.75 - 1.00)
t _{max} (hr)	1.1 (30)	0.9 (31)	N/A
t _{1/2} (hr)	2.2 (29)	2.2 (28)	N/A

¹ Mean (%CV)
PK parameters are presented as mean (%CV); AUC_{ss} = Steady-state AUC; C_{max} = Maximum plasma concentration; C_{min} = Minimum plasma concentration; t_{max} = Time to C_{max}; t_{1/2} = Terminal phase half-life

Conclusions

- Zidovudine has no effect on the PK of emtricitabine
- Coadministration of emtricitabine with zidovudine increased AUC_{ss} and C_{max} of zidovudine by 13% and 17%, respectively. Such small increases in the exposure of zidovudine following emtricitabine coadministration are unlikely to be clinically significant
- Emtricitabine and zidovudine were generally well tolerated when administered alone and together in this healthy volunteer population