

## Introduction

- Tenofovir DF (TDF) is approved for use in the treatment of HIV-infected adults
- TDF has in vitro and in vivo activity against Hepatitis B virus (HBV)<sup>1</sup>
- Hepatic impairment (HI) is a significant co-morbidity in patients with HIV-1 and is common in patients with HBV and/or Hepatitis C virus (HCV) co-infection
- Three studies were conducted to evaluate tenofovir PK, drug interaction (DI) potential, and safety of TDF in the hepatically impaired and drug interaction potential with drugs used in HIV-1 co-infected populations

## Objective

- Study 1: To evaluate the pharmacokinetics (PK) of tenofovir in HI
- Study 2: To evaluate the drug interaction potential of TDF and adefovir dipivoxil (ADV) which is used for the treatment of chronic hepatitis B (CHB)
- Study 3: To evaluate the drug interaction potential of TDF and ribavirin (RBV) which is used in the treatment of chronic HCV
- Safety of single or multiple doses of TDF given alone and co-administered with ADV or RBV was also assessed

## Methods

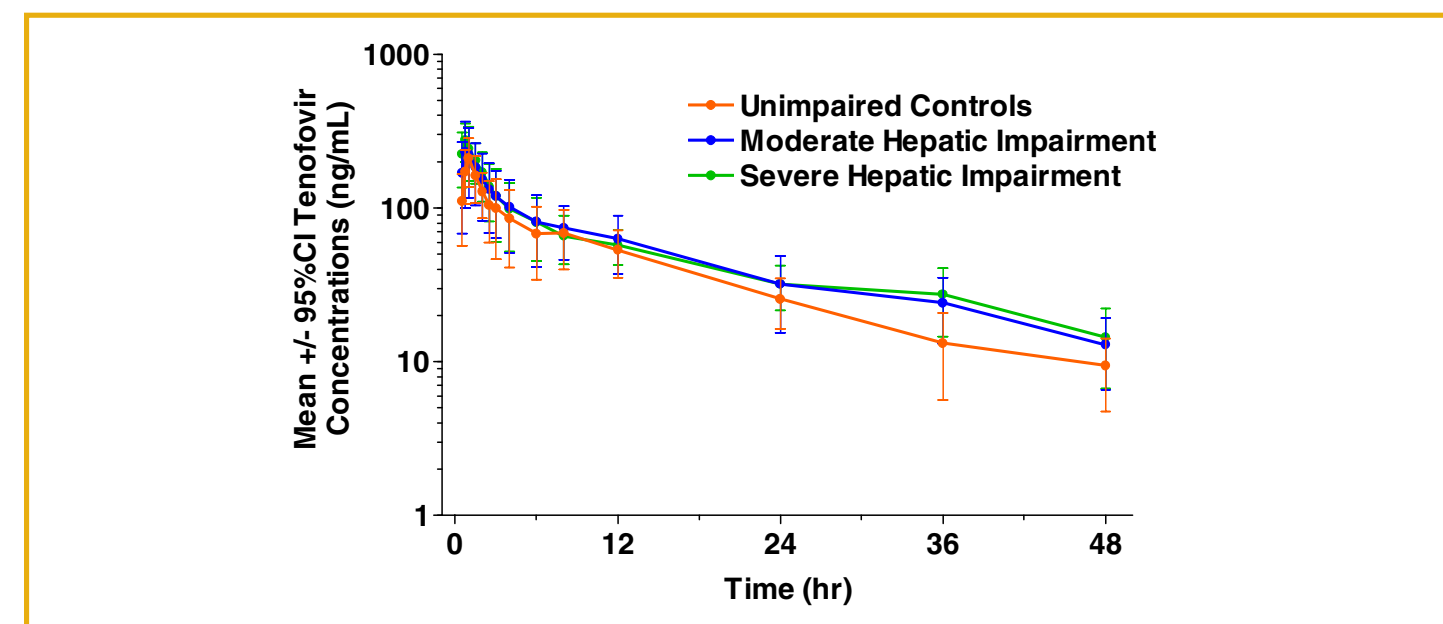
- Study 1: A single 300 mg dose of TDF was administered orally to otherwise healthy subjects with HI due to non-HBV/HCV etiologies
  - Tenofovir PK was evaluated in those with normal hepatic function or moderate or severe HI, stratified by Child-Pugh-Turcotte score
- Study 2: PK of adefovir was evaluated in healthy subjects following a single dose of ADV 10 mg alone (Day 1) and following multiple doses of TDF 300 mg (Day 8)
- Study 3: PK of RBV 600 mg was evaluated in healthy subjects following a single dose of RBV alone (Day 1) and again following multiple doses of TDF 300 mg (Day 22)
- Blood sampling was performed over 24- (Study 2), 48- (Study 1) and 72-hours (Study 3) post-dose
- Tenofovir concentrations in serum/plasma were determined by validated LC/MS/MS assays
- PK parameters estimated by noncompartmental methods using WinNonlin<sup>TM</sup>
- In DI studies, C<sub>max</sub> and AUC results reported as 90% confidence intervals about the ratio of geometric means [GMR (90% CI)] for ADV or RBV + TDF vs. ADV or RBV alone
  - No change in PK concluded if 90% CI of GMR lies within 80%-125% range
- Safety was evaluated by physical examination, clinical adverse events (AE), and laboratory assessments

**Table 1. Study 1: Tenofovir PK in Hepatic Impairment (n = 23)**

Tenofovir Pharmacokinetic Parameters	Unimpaired Controls (n = 8)	Moderate Impairment (n = 7)	Severe Impairment (n = 8)
Child-Pugh-Turcotte Score: Class:	5.0 ± 0.0 A	8.0 ± 0.8 B	10.8 ± 1.0 C
AUC <sub>0-t</sub> (ng•hr/mL) (min-max)	1820 (47.2%) (956 - 3540)	2040 (41.9%) (1140 - 3790)	2300 (35.8%) (1403 - 3920)
AUC <sub>0-∞</sub> (ng•hr/mL) (min-max)	2050 (50.8%) (1090 - 4060)	2310 (43.5%) (1220 - 4340)	2740 (43.9%) (1460 - 5230)
C <sub>max</sub> (ng/mL) (min-max)	223 (34.7%) (120 - 353)	289 (46.0%) (163 - 552)	305 (24.8%) (210 - 440)
T <sub>1/2</sub> (hr) (min-max)	17.3 (10.1 - 23.2)	17.0 (13.1 - 19.3)	18.0 (9.74 - 26.5)
T <sub>max</sub> (hr) (min-max)	1.00 (0.50 - 1.00)	1.00 (0.50 - 1.00)	0.75 (0.50 - 2.00)

AUC<sub>0-t</sub> = area under the curve over 48 hours, AUC<sub>0-∞</sub> = area under the curve to infinite time; C<sub>max</sub> = maximum serum concentration; T<sub>1/2</sub> = terminal elimination half-life, T<sub>max</sub> = time to C<sub>max</sub>  
Data expressed as arithmetic mean (CV%) and (min-max) or median (min-max)

**Figure 1. Tenofovir Concentration - Time Profiles**



- Tenofovir PK are not significantly altered in subjects with HI relative to those with normal liver function

**Table 2. Study 2: Adefovir PK with TDF (n = 22)**

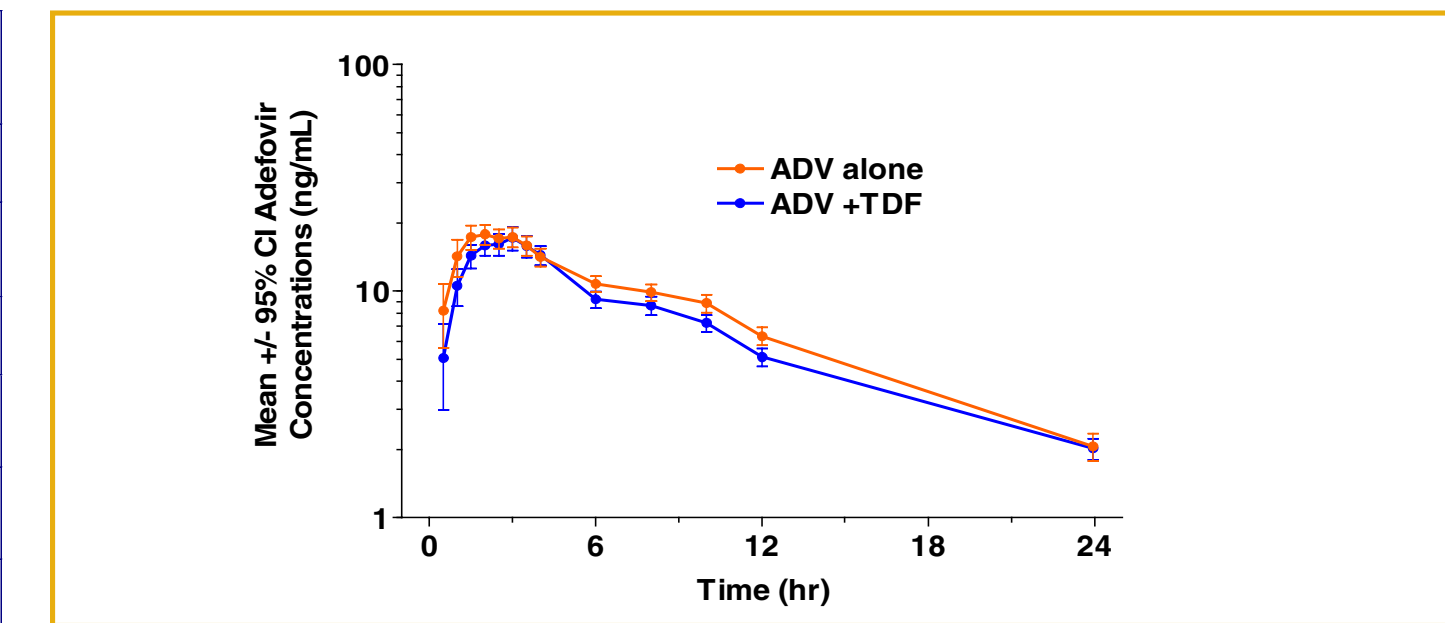
Adefovir Pharmacokinetic Parameters	ADV alone	ADV + TDF	% Mean Ratio (90% CI)
AUC <sub>0-t</sub> (ng•hr/mL)	181 (20.6%)	159 (18.7%)	88.3 (84.8, 91.9)
AUC <sub>0-∞</sub> (ng•hr/mL)	200 (39.6%)	183 (19.1%)	89.4 (85.7, 93.3)
C <sub>max</sub> (ng/mL)	19.3 (23.2%)	18.0 (24.8%)	93.1 (86.9, 99.8)
T <sub>1/2</sub> (hr)	7.09 (5.75 - 9.52)	7.83 (6.65 - 10.1)	NA
T <sub>max</sub> (hr)	2.00 (1.00 - 4.03)	2.25 (1.00 - 4.01)	NA

AUC<sub>0-t</sub> = area under the curve over 24 hr, AUC<sub>0-∞</sub> = area under the curve to infinite time; C<sub>max</sub> = maximum plasma concentration; T<sub>1/2</sub> = terminal elimination half-life, T<sub>max</sub> = time to C<sub>max</sub>  
Data expressed as arithmetic mean (%CV) or median (min-max)  
% Geometric mean ratio is the model-based anti-log of the difference of the treatment of ADV + TDF vs. ADV alone (90% confidence interval of the ratio)

- Adefovir PK are not significantly altered when ADV is dosed with TDF

## Results

**Figure 2. Adefovir Concentration - Time Profiles**



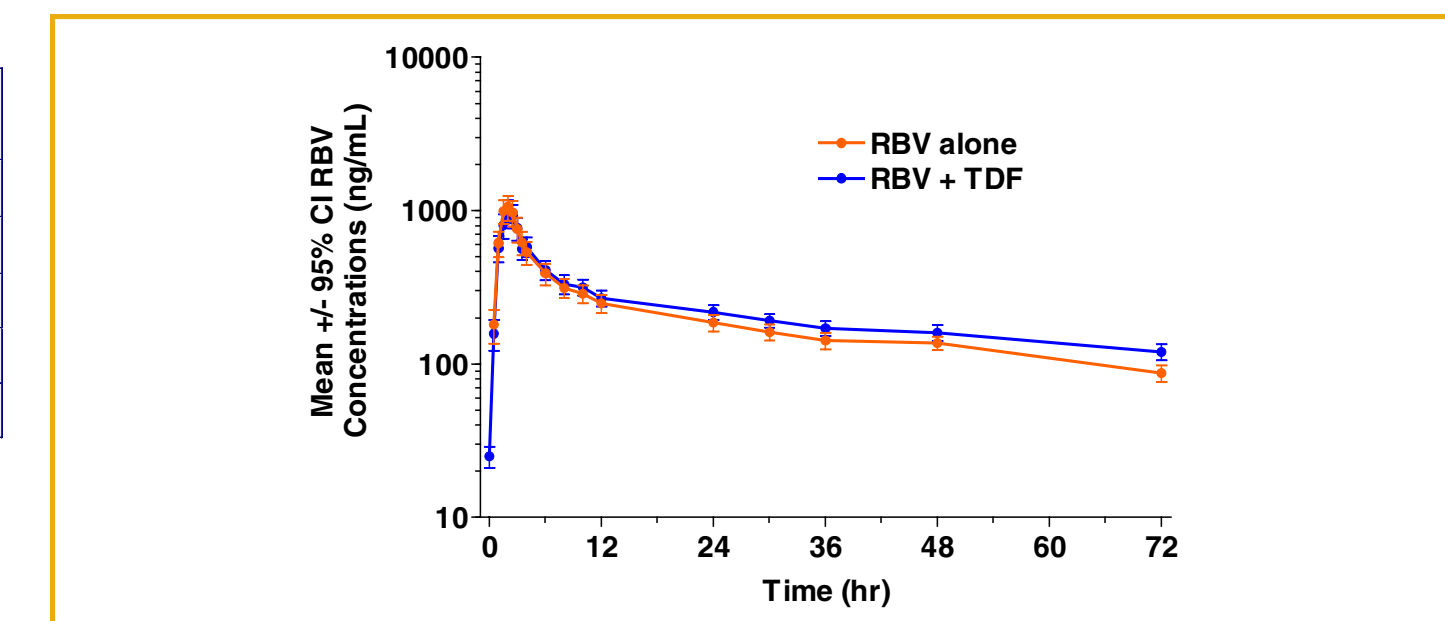
**Table 3. Study 3: Ribavirin PK with TDF (n = 22)**

- Due to a long RBV half-life there was carry-over from the day 1 dose of RBV on day 22 (+ TDF) with quantifiable RBV concentrations in pre-dose samples of all subjects. No adjustments for carry over were performed.
- RBV PK are unaltered when dosed with TDF
  - RBV C<sub>max</sub> and AUC<sub>0-t</sub> met the definition of PK equivalence ± TDF
  - When carry-over of RBV is accounted for the % mean ratio for RBV AUC<sub>0-t</sub> ± TDF = 100%

Ribavirin Pharmacokinetic Parameters	RBV alone	RBV + TDF	% Mean Ratio (90% CI)
AUC <sub>0-t</sub> (µg•hr/mL)	14.3 (28.8%)	16.0 (25.7%)	112 (106, 117)
C <sub>max</sub> (µg/mL)	1.12 (40.2%)	1.04 (35.2%)	94.6 (88.7, 101)
T <sub>1/2</sub> (hr)	48.1 (35.7 - 70.3)	61.6 (35.2 - 72.5)	NA
T <sub>max</sub> (hr)	2.00 (1.48 - 3.50)	2.00 (1.50 - 3.00)	NA

AUC<sub>0-t</sub> = area under the curve over 72 hr; C<sub>max</sub> = maximum plasma concentration; T<sub>1/2</sub> = terminal elimination half-life, T<sub>max</sub> = time to C<sub>max</sub>  
Data expressed as arithmetic mean (%CV) or median (min-max)  
% Geometric mean ratio is the model-based anti-log of the difference of the treatment of RBV + TDF vs. RBV alone (90% confidence interval of the ratio)

**Figure 3. Ribavirin Concentration - Time Profiles**



## Safety Results

- Study 1: PK in Hepatic Impairment, 24 subjects enrolled, 22 completed
  - 8/24 subjects (33%) experienced at least 1 treatment-emergent AE
  - Grade 1-2 headache (n = 2) and decreased urine volume (n = 2) were the most common AEs
  - One subject with severe hepatic impairment died of septic shock 10 days following TDF dosing. This was considered unrelated to study drug
  - There were no other Grade 3/4 or serious AEs
- Study 2: TDF/ADV Drug Interaction, 24 subjects enrolled, 22 completed
  - 15/24 subjects (63%) experienced at least 1 treatment-emergent AE
  - Grade 1 headache and nausea were the most common AEs
  - 2 subjects were discontinued due to vomiting during dosing TDF alone; these events were considered related to study drug
  - No Grade 2-4 or serious AEs reported
- Study 3: TDF/RBV Drug Interaction, 23 subjects enrolled, 22 completed
  - 18/23 subjects (78%) experienced at least 1 treatment-emergent AE
  - Headache and nausea (Grade 1-2) were most common AE reported
  - One subject was discontinued from the trial due to the serious AEs of cholecystitis and pancreatitis 16 days following dosing RBV alone. These serious AEs were considered unrelated to study treatment
  - No other Grade 2-4 or serious AEs reported

## Conclusions

- Tenofovir PK are not significantly altered in subjects with moderate or severe hepatic impairment
  - No dose adjustment of TDF is required
- The PK of adefovir was equivalent when dosed with or without TDF
- The PK of RBV was equivalent when dosed with or without TDF

## References

- D Cooper, G Dore, A Pozniak, et al, for the 903 Study Team. Tenofovir Disoproxil Fumarate and Lamivudine Combination Therapy Compared to Lamivudine Alone for HBV in Therapy-Naïve HIV/HBV Co-Infected Patients: 48 Week Interim Results. 10<sup>th</sup> Conference on Retroviruses and Opportunistic Infections. Boston, MA. Feb 2003 [poster 825].