GILEAD | Medical Information

Vemlidy® (tenofovir alafenamide) Coadministration With Rifampin

This document is in response to your request for information regarding the coadministration of Vemlidy® (tenofovir alafenamide [TAF]) with rifampin (RIF).

Some data may be outside of the US FDA-approved prescribing information. In providing this data, Gilead Sciences, Inc. is not making any representation as to its clinical relevance or to the use of any Gilead product(s). For information about the approved conditions of use of any Gilead drug product, please consult the FDA-approved prescribing information.

The full indication, important safety information, and boxed warnings are available at: www.gilead.com/-/media/files/pdfs/medicines/liver-disease/vemlidy/vemlidy_pi.

PK DDI Evaluation

Drug interaction studies have not been conducted between the single-tablet regimen TAF and RIF. Based on the PK profile of each active ingredient within TAF and RIF, a PK interaction would be predicted. Coadministration is not recommended due to the induction of P-gp by RIF, which would be expected to decrease TAF plasma concentration. For more information about RIF, please refer to its product labeling.[1,2]

TAF PK[1]

DDI Mechanism		TAF
Drug Transporters	P-gp/BCRP	Substrate
	OATP1B1	N/A
	OATP1B3	N/A
Drug Metabolizing Enzymes	CYP1A2	N/A
	CYP2C8/9/19	N/A
	CYP2D6	N/A
	CYP3A4	N/A

Relevant TAF Label Information[1]

Coadministration of TAF with the P-gp inducers rifabutin, rifampin or rifapentine is not recommended. Coadministration with these agents leads to decreased TAF concentrations.

PK Studies on TAF-Containing Regimen With RIF

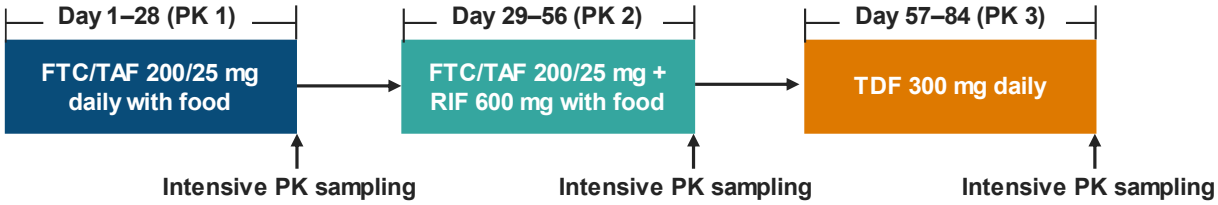
Phase 1 Study of FTC/TAF With RIF[3]

Study design and demographics

A phase 1, open-label, single-center study was conducted to evaluate the PK of FTC/TAF 200/25 mg during coadministration with RIF 600 mg in 21 healthy adult volunteers.

At baseline, the mean age was 33 years, 67% were female, 53% were White, 33% were of African ancestry, and the mean BMI was 26 kg/m^2.

Figure 1. Study Design (Cerrone et al)[3]



PK results

RIF coadministered with FTC/TAF decreased TAF plasma C_{max} and $AUC_{0–24\ h}$ by 50% and 55%, respectively. Plasma TFV C_{max}, $C_{24\ h}$, and $AUC_{0–24\ h}$ were reduced by 65%, 55%, and 54%, respectively. Intracellular TFV-DP C_{max}, $C_{24\ h}$, and $AUC_{0–24\ h}$ were decreased by 38%, 43%, and 36%, respectively. However, intracellular TFV-DP PK GMRs with FTC/TAF + RIF were over 4-fold higher when compared with those observed when TDF was administered without RIF (Table 1).

Table 1. Plasma TAF, TFV, and Intracellular TFV-DP GMRs of Key PK Parameters of FTC/TAF ± RIF and TDF Alone (Cerrone et al)[3]

PK Parameter, GMR (90% CI)	FTC/TAF + RIF vs FTC/TAF			FTC/TAF + RIF vs TDF
	TAF	TFV	TFV-DP	TFV-DP
C_{max}	0.5 (0.42–0.61)	0.35 (0.3–0.42)	0.62 (0.52–0.74)	4.4 (3.09–6.27)
$C_{24\ h}$	–	0.45 (0.42–0.5)	0.57 (0.47–0.71)	4.15 (2.89–5.94)
$AUC_{0–24\ h}$	0.45 (0.33–0.6)	0.46 (0.4–0.52)	0.64 (0.54–0.75)	4.21 (2.98–5.95)

Safety

Overall, FTC/TAF ± RIF was well tolerated. Two healthy volunteers discontinued the study: 1 discontinued due to an increase in ALT, which was deemed unrelated to study drug, and the other withdrew consent following Grade 2 RIF-related gastrointestinal symptoms. No Grade 3 or 4 AEs, serious AEs, or deaths were reported.

Phase 1 Study of BIC/FTC/TAF With RIF[4]

Study design and demographics

A phase 1, open-label, parallel-design, single-center study in healthy volunteers was conducted to compare the PK, safety, and tolerability of TAF with or without RIF. TAF was

administered as a BIC/FTC/TAF 50/200/25 mg single-tablet regimen either once daily (Cohort 1; n=26) or twice daily with RIF 600 mg once daily (Cohort 2; n=26) for 28 weeks.

Baseline demographics for Cohort 1 and Cohort 2 were well balanced: mean age, 35 years vs 36 years, respectively; female, 50% vs 50%; Black, 23% vs 23%; mean BMI, 26.2 kg/m^2 vs 26 kg/m^2; and mean $eGFR_{CG}$, 129 mL/min vs 130 mL/min.

PK results

Following twice daily administration of BIC/FTC/TAF with RIF in Cohort 2 and relative to once daily BIC/FTC/TAF administration in Cohort 1, plasma $AUC_{0–24\ h}$ was expected to be reduced by ~14% for TAF, ~20% for TFV, and ~24% for intracellular peripheral blood mononuclear cells-associated TFV-DP (Table 2).

Table 2. BIC/FTC/TAF Once Daily vs BIC/FTC/TAF Twice Daily + RIF: Plasma TAF, TFV and Intracellular TFV-DP PK (Custodio et al)[4]

$AUC_{0–24\ h}$	BIC/FTC/TAF Once Daily (n=26)	BIC/FTC/TAF Twice Daily + RIF Once Daily (n=26)	GLSM Ratio (90% CI)
TAF, mean (%CV), ng·h/mL	345 (52)	290 (48)	85.8 (69.7–106)
TFV, mean (%CV), ng·h/mL	348 (20)	277 (19)	79.9 (73.1–87.3)
TFV-DP, fmol·h/10^6 cells	N/A	N/A	76.3 (58.7–99.2)

Abbreviations: CV=coefficient of variation; GLSM=geometric least squares mean.

Safety

All treatments were generally well tolerated, and all healthy volunteers completed the study. All AEs were mild or moderate in severity and resolved during the study. Occurrence of treatment-emergent AEs was generally balanced across cohorts: Cohort 1, 31% vs Cohort 2, 39%. No Grade 3 or 4 AEs and no laboratory abnormalities were observed.

References

1. Enclosed. Gilead Sciences Inc, VEMLIDY® (tenofovir alafenamide) tablets, for oral use. U.S. Prescribing Information. Foster City, CA.
2. RIFADIN, Sanofi-Aventis U.S. LLC. RIFADIN- Rifampin Capsule. RIFADIN IV- Rifampin Injection, Powder, Lyophilized, for Solution. U. S. Prescribing Information. Bridgewater, NJ.
3. Cerrone M, Alfarisi O, Neary M, et al. Rifampicin Effect on Intracellular and Plasma Pharmacokinetics of Tenofovir Alafenamide. *J Antimicrob Chemother.* 2019. https://www.ncbi.nlm.nih.gov/pubmed/30815689
4. Custodio J, West SK, Lutz J, et al. Twice Daily Administration of Tenofovir Alafenamide in Combination with Rifampin: Potential for Tenofovir Alafenamide Use in HIV-TB Coinfection [Presentation]. Paper presented at: European AIDS Clinical Society (EACS); 25-27 October, 2017; Milan, Italy.

Abbreviations

AE=adverse event
$AUC_{0–24\ h}$=area under the concentration-time curve from time 0 to 24 hours
BCRP=breast cancer resistance protein
BIC=bictegravir
$C_{24\ h}$=plasma concentration at 24 hours
CG=Cockcroft-Gault
C_{max}=maximum plasma concentration
DDI=drug-drug interaction
FTC=emtricitabine
GMR=geometric mean ratio
OATP=organic anion transporting polypeptide
P-gp=P-glycoprotein
PK=pharmacokinetic(s)
RIF=rifampin
TAF=tenofovir alafenamide
TDF=tenofovir disoproxil fumarate
TFV=tenofovir
TFV-DP=tenofovir diphosphate

Product Label

For the full indication, important safety information, and boxed warning(s), please refer to the Vemlidy US Prescribing Information available at: www.gilead.com/~/media/files/pdfs/medicines/liver-disease/vemlidy/vemlidy_pi.

Follow-Up

For any additional questions, please contact Gilead Medical Information at:

☎1-866-MEDI-GSI (1-866-633-4474) or 🖱 www.askgileadmedical.com

Adverse Event Reporting

Please report all adverse events to:

Gilead Global Patient Safety ☎ 1-800-445-3235, option 3 or
🖱 www.gilead.com/utility/contact/report-an-adverse-event

FDA MedWatch Program by ☎ 1-800-FDA-1088 or ✉MedWatch, FDA, 5600 Fishers Ln, Rockville, MD 20852 or 🖱 www.accessdata.fda.gov/scripts/medwatch

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