GILEAD | Medical Information

Descovy® (FTC/TAF) Coadministration with Rifamycins

This document is in response to your request for information regarding Descovy® (emtricitabine/tenofovir alafenamide [FTC/TAF]) and coadministration with rifamycins, specifically RIF (rifampin), rifabutin, and RPT (rifapentine).

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/hiv/descovy/descovy_pi; www.gilead.com/-/media/files/pdfs/medicines/hiv/biktarvy/biktarvy_pi.

Summary

Product Labeling[1]

Concomitant use of FTC/TAF and rifabutin, RIF, or RPT decreases the concentration of TAF. Coadministration is not recommended.

PK Data[1]

TAF, a component of FTC/TAF, is a substrate of P-gp. Drugs that induce P-gp activity are expected to decrease the absorption of TAF, resulting in decreased plasma concentration of TAF, which may lead to loss of therapeutic effect of FTC/TAF and development of resistance.

Clinical Data

- In a phase 1, open-label study, co-administration of RIF with FTC/TAF decreased intracellular TFV-DP concentrations by 36% compared with FTC/TAF alone.[2]
- In a phase 1, open-label study with a parallel design, decreases of 15% to 24% in the $AUC_{0\text{-}24h}$ were observed for TAF, TFV, and intracellular TFV-DP with the administration of TAF twice daily + RIF than with TAF daily.[3]
- All treatments were generally well-tolerated in both studies.[2,3]

Product Labeling[1]

Concomitant use of FTC/TAF and rifabutin, RIF, or RPT decreases the concentration of TAF. Coadministration is not recommended (Table 1).

Table 1. Established and Other Potentially Significant[a] Drug Interactions[1]

Concomitant Drug Class: Drug Name	Effect on Concentration[b]	Clinical Comment
Antimycobacterials: Rifabutin RIF RPT	↓ TAF	Coadministration of FTC/TAF with rifabutin, RIF, or RPT is not recommended.

[a]This table is not all inclusive.
[b]↓=decrease.

PK Data[1]

TAF, a component of FTC/TAF, is a substrate of P-gp. Drugs that induce P-gp activity are expected to decrease the absorption of TAF, resulting in decreased plasma concentration of TAF, which may lead to loss of therapeutic effect of FTC/TAF and development of resistance.

Clinical Data

PK of FTC/TAF Administered in Combination with RIF Compared with FTC/TAF and TDF[2]

Study design and baseline demographics

A phase 1, open-label, single-center study with three sequential phases was conducted in 23 HIV-negative healthy volunteers to assess the PK, safety, and tolerability during administration of FTC/TAF, FTC/TAF + RIF, and TDF (Figure). Healthy volunteers started on FTC/TAF daily for 28 days, which was given with a standard meal that contained 20g of fat content. Starting on Day 29, participants received RIF daily administered 30 minutes before a standard meal followed by FTC/TAF for 28 days (Days 29–56). On Day 57, participants discontinued FTC/TAF + RIF and started TDF monotherapy daily for 28 days (Days 57–84), which was administered with a standard meal. Steady-state plasma concentrations were measured weekly from Days 7 to 56 for TAF, TDF, FTC, and the respective metabolites. Baseline demographics of the 21 volunteers who completed the study are shown in Table 2.

Figure 1. Study Design[2]

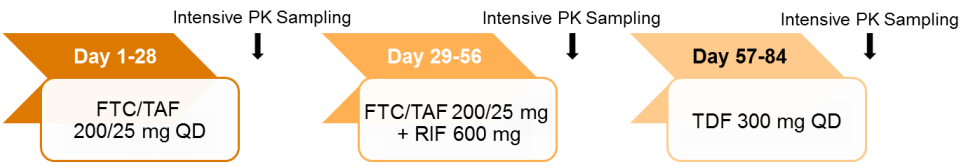

Table 2. Baseline Demographics[2]

Key Demographics and Characteristics	Evaluable Healthy Volunteers (N=21)
Age, mean (range), year	33 (22–58)
Male sex, %	33
Ethnicity	
African ancestry, %	33
White, %	53
Other, %	14
BMI, mean (range), kg/m^2	26 (19–35)

PK results

Compared to FTC/TAF, coadministration of RIF with FTC/TAF decreased the plasma TAF C_{max} by 50% and the TAF $AUC_{0\text{-}24h}$ by 55%; intracellular TFV-DP C_{max} decreased by 38% and $AUC_{0\text{-}24h}$ decreased by 36%. However, intracellular TFV-DF concentrations were 4-fold higher with FTC/TAF + RIF than with TDF monotherapy (Table 3). RIF coadministration did not alter plasma FTC or intracellular FTC-triphosphate concentrations.

Table 3. Summary of PK Parameters[2]

PK Parameters	FTC/TAF + RIF vs FTC/TAF	FTC/TAF + RIF vs TDF Monotherapy
TAF C_{max}, GMR (90% CI)	0.50 (0.42–0.61)	-
TAF $AUC_{0\text{-}24h}$, GMR (90% CI)	0.45 (0.33–0.60)	-
TFV-DP C_{max}, GMR (90% CI)	0.62 (0.52–0.74)	4.40 (3.09–6.27)
TFV-DP $AUC_{0\text{-}24h}$, GMR (90% CI)	0.64 (0.54–0.75)	4.21 (2.98–5.95)

Abbreviation: GMR=geometric mean ratio.

Safety and tolerability results

FTC/TAF ± RIF and TDF monotherapy were well-tolerated. There were 2 discontinuations: 1 case of transient increase in ALT levels (≥8 times the upper limit of normal) during the FTC/TAF-only phase, which was deemed unlikely to be TAF-related by the study investigators, and 1 case of Grade 2 gastrointestinal symptoms, which were deemed RIF-related by the study investigators. There were 2 AEs documented during the study (both Grade 3), and no Grade 4 AEs were observed.

PK of TAF Administered Twice Daily in Combination with RIF

Study design and baseline demographics

A phase 1, open-label, parallel-design, multiple-dose, single-center study was conducted to evaluate the safety, tolerability, and steady-state PK of TAF, intracellular TFV-DP, and TFV, the major TAF metabolite, following administration of TAF 25 mg daily (Cohort 1; n=26) compared with coadministration of TAF 25 mg twice daily + RIF 600 mg daily (Cohort 2; n=26) in healthy volunteers.[3] TAF was administered as a part of the single tablet regimen

BIC/FTC/TAF. FTC/TAF is not FDA-approved for twice daily dosing.[1] Baseline demographics were similar between study groups (Table 4).[3]

Table 4. Baseline Demographics[3]

Key Demographics and Characteristics	TAF Daily (n=26)	TAF Twice Daily + RIF (n=26)
Age, mean, years	35	36
Female sex, %	50	50
Race		
Black, %	23.1	23.1
White, %	76.9	76.9
BMI, mean, kg/m^2	26.2	26
$eGFR_{CG}$, mean, mL/min	129	130

Abbreviation: $eGFR_{CG}$=estimated glomerular filtration rate by Cockcroft-Gault.

Safety results

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

PK results

After administration of TAF twice daily + RIF, TAF plasma AUC_{0-24} is expected to be reduced by <15% compared with TAF daily. TFV AUC_{0-24} is expected to be approximately 20% lower following administration of TAF twice daily + RIF vs TAF daily. Following administration of TAF twice daily + RIF, the AUC_{0-24} of the intracellular peripheral blood mononuclear cell associated TFV-DP is expected to be decreased by approximately 24% vs TAF daily (Table 5).[3]

Table 5. Plasma TAF, Intracellular TFV-DP, and TFV PK Following TAF Twice Daily + RIF vs TAF Daily[3]

AUC_{0-24}	Cohort 1: TAF Daily (n=26)	Cohort 2: TAF Twice Daily + RIF (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)
Intracellular 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; N/A=not available.

References

1. Enclosed. Gilead Sciences Inc, DESCOVY® (emtricitabine and tenofovir alafenamide) tablets, for oral use. U.S. Prescribing Information. Foster City, CA.

2. Cerrone M, Alfarisi O, Neary M, et al. Rifampicin Effect on Intracellular and Plasma Pharmacokinetics of Tenofovir Alafenamide. *J Antimicrob Chemother.* 2019;74(6):1670-1678.
3. 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 effect
AUC=area under the curve
$AUC_{0\text{-}24h}$=area under the curve over 24 hours
BIC=bictegravir
C_{max}=maximum concentration
FTC=emtricitabine
P-gp=P-glycoprotein
PK=pharmacokinetics
RIF=rifampin
RPT=rifapentine
TAF=tenofovir alafenamide
TDF=tenofovir disoproxil
TFV=tenofovir
TFV-DP=tenofovir diphosphate

Product Label

For the full indication, important safety information, and boxed warning(s), please refer to the Descovy and Biktarvy US Prescribing Information available at:
www.gilead.com/-/media/files/pdfs/medicines/hiv/descovy/descovy_pi;
www.gilead.com/-/media/files/pdfs/medicines/hiv/biktarvy/biktarvy_pi.

Follow Up

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