

No Clinically Relevant Effect of Patient Demographic or Disease Covariates on the Exposures of Bictegravir and Tenofovir Alafenamide Following Administration of a B/F/TAF Single-Tablet Regimen to HIV-1–Infected Patients



Justin D. Lutz,¹ Brian J. Kirby,¹ Yongwu Shao,¹ Yuying Gao,² Erin Quirk,¹ Anita Mathias¹

¹Gilead Sciences, Inc., Foster City, California, USA; ²Certara Strategic Consulting, Menlo Park, California

Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, California, USA 94404
800-445-3235

Introduction

- Bictegravir (BIC)/emtricitabine/tenofovir alafenamide (B/F/TAF 50/200/25 mg) is a single tablet regimen (STR) approved in Australia, Canada, EU, and USA for treatment of HIV-1 infection in treatment-naïve and virologically suppressed adults without resistance to its components¹
 - B/F/TAF is a Department of Health and Human Services and International Antiviral Society guidelines-recommended initial regimen for most HIV-1–infected patients²
 - B/F/TAF requires qd dosing without regard to food, and has limited testing requirements prior to initiation and few known drug-drug interactions
- In five Phase 3 studies of HIV-1–infected patients, B/F/TAF was safe and efficacious, with no development of resistance³⁻⁷
- A population-based pharmacokinetic (PK) model was developed to understand the clinical covariates of the PK of BIC and TAF in HIV-1–infected patients when administered as B/F/TAF 50/200/25 mg qd

Objectives

- To determine the effects of demographic, pathophysiologic, and HIV-1–related covariates on the PK of BIC and TAF to better understand clinical factors that may affect exposure in individual patients

Methods

Population PK Modeling

- Population PK models for BIC and TAF were developed using pooled intensive and sparse plasma concentration data (8752 and 4201 observations, respectively) from 18 Phase 1 and 3 studies in healthy volunteers (HVs) and patients with HIV-1 infection (BIC: n=1318; TAF: n=1409)
 - A nonlinear mixed-effects modeling approach using a 1st-order conditional estimation with interaction method in NONMEM[®] 7.3 (ICON plc, Dublin, Ireland) was employed

Covariate Effects

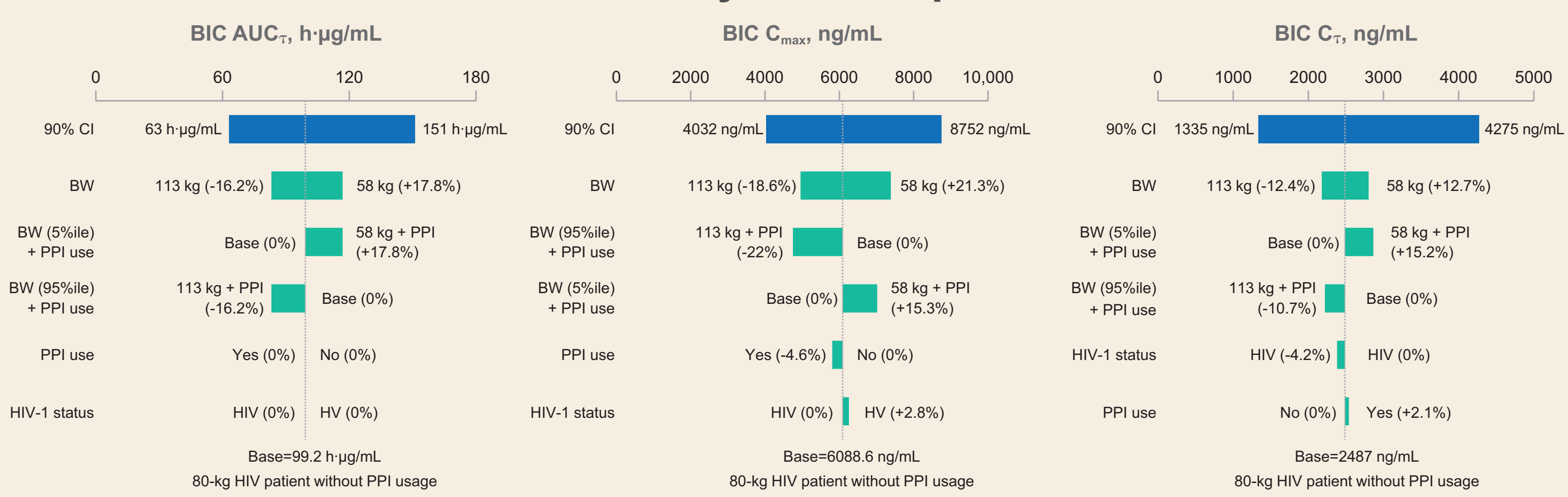
- Significance covariates were determined using a forward addition and backward elimination method (based on significance levels of $p < 0.01$ and $p < 0.001$, respectively)
 - Demographics: baseline age, sex, race (white vs black or African-American vs Asian vs other), body weight (BW), and HIV-1 status (HVs vs HIV-1–infected patients)
 - Pathophysiologic covariates: baseline creatinine clearance, prior treatment experience (naïve vs experienced), and concomitant administration of H2-receptor antagonists (H2RAs) or proton pump inhibitors (PPIs)
 - Other covariates: fasting/fed status (never vs sometimes vs always fed) and baseline hepatitis B or C virus (HBV or HCV, respectively) coinfection status
- To examine the influence of patient covariates on the steady-state exposures of BIC (area under plasma concentration-time curve over dosing interval [AUC_τ], maximum plasma concentration [C_{max}], and concentration at end of dosing interval [C_τ]) and TAF (AUC_τ and C_{max}):
 - Sensitivity analyses of significant covariates were performed
 - Exposures were stratified by covariate and compared

Results

- The developed population PK models adequately described BIC and TAF PK (data on file)
 - BIC PK was described using a 1-compartment model, with 1st-order absorption, a lag time, and 1st-order elimination from the central compartment
 - Only HIV-1 status, BW, and baseline PPI status were identified as statistically significant covariates
 - TAF PK was described by a 2-compartment model with sequential 0- then 1st-order absorption, with 1st-order elimination from the central compartment and redistribution from the peripheral compartment
 - Only HIV-1 status and sex on clearance were identified as statistically significant covariates

BIC Sensitivity Analysis

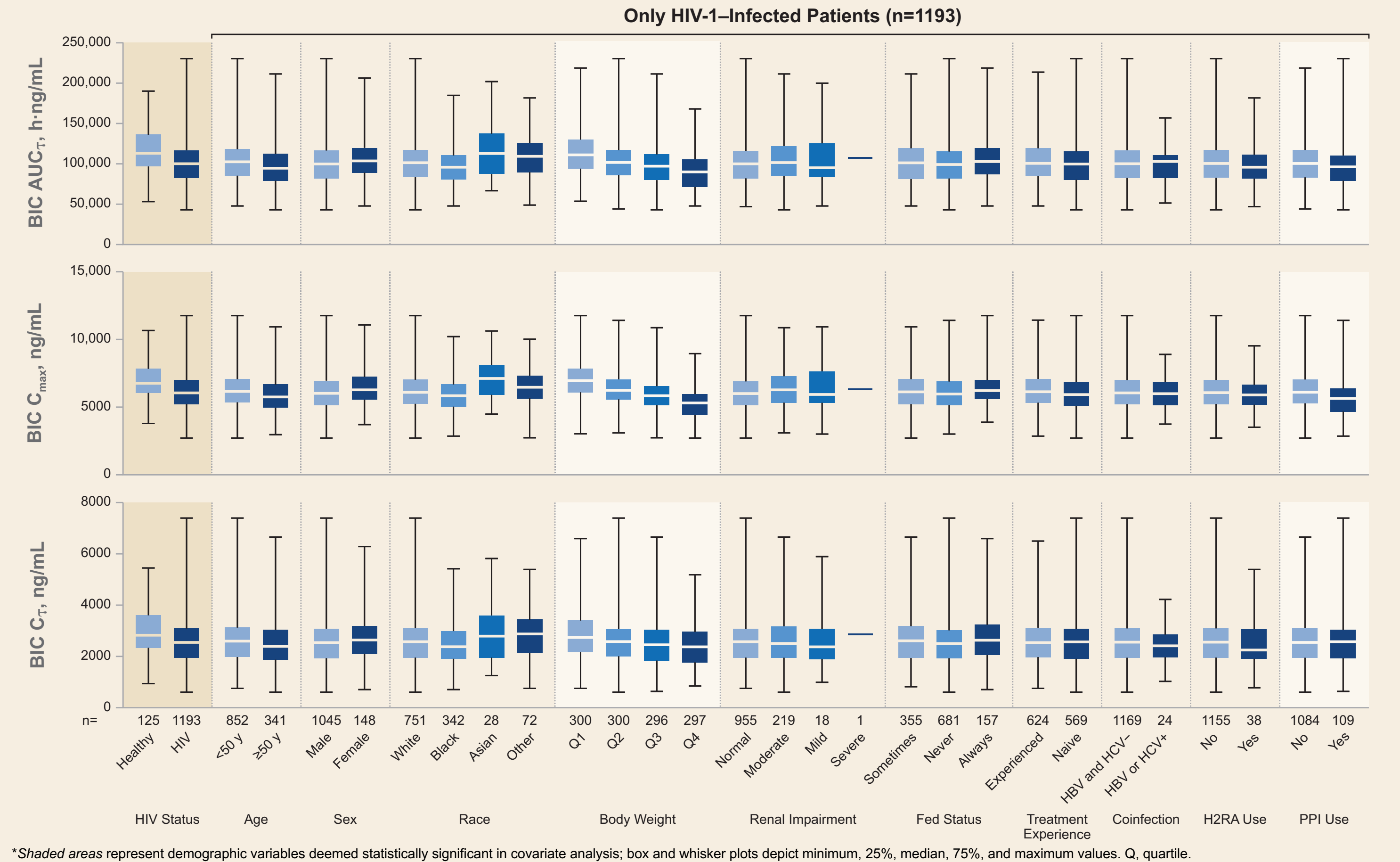
Effect of Covariates on BIC Steady-State Exposure*



- The sensitivity analysis showed that baseline BW was the greatest contributor to the variability of BIC exposure (34% for AUC_τ across 90% of plausible range of BW)
- The contribution of HIV-1 status or baseline PPI use to the variability in BIC exposure was low (<5%)

BIC Exposure Summary in HVs and Phase 3 Population

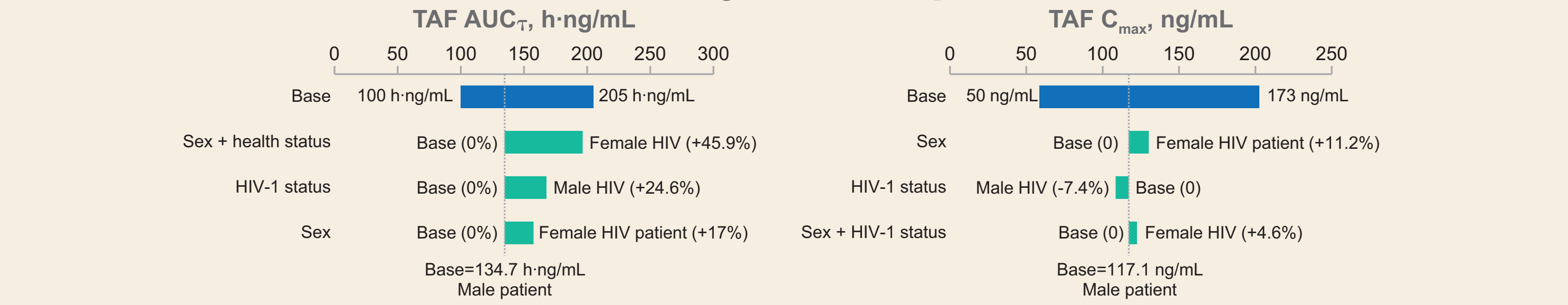
Effect of HIV-1 Infection Status or Demographic Variables on BIC PK in Phase 3 Population (HIV-1–infected patients) Administered B/F/TAF STR*



- Mean BIC exposures in HVs (n=125) and HIV-1–infected patients (n=1193) differed by 12–13%
- Mean BIC exposures in highest (n=297) and lowest (n=300) BW quartiles differed by 17–26%
- Mean BIC exposures in patients with (n=109) and without (n=1084) concomitant PPI administration differed by <9%
- All other demographic and disease covariates demonstrated minimal-to-no effects on BIC exposure

TAF Sensitivity Analysis

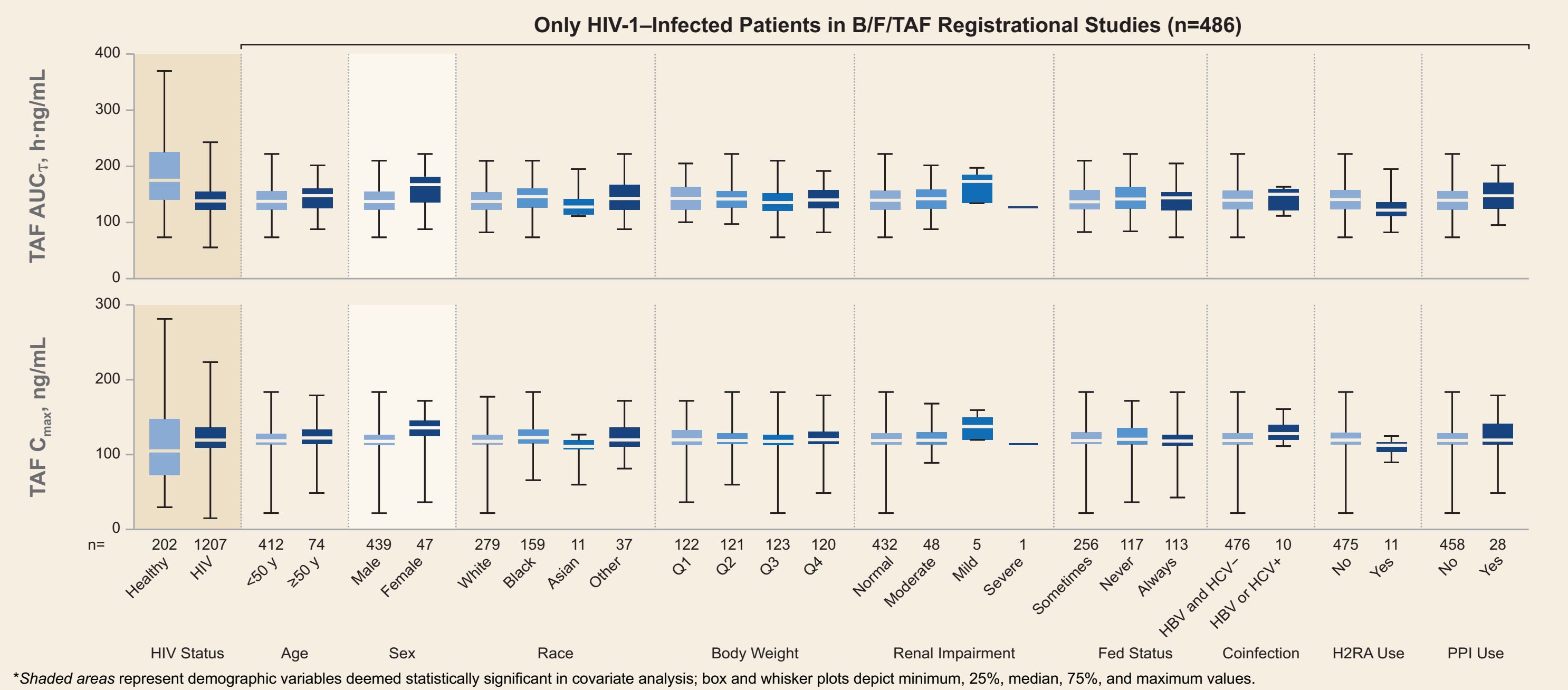
Effect of Covariates on TAF Steady-State Exposure*



- The sensitivity analysis showed that the contribution of HIV-1 status or sex to variability in TAF exposure was low (7–25%), but the combination of both sex and HIV-1 status explained 11–46% of variability in TAF exposure

TAF Exposure Summary in HVs and Phase 3 Registrational Studies

Effect of HIV-1 Infection Status or Demographic Variables on TAF PK in Phase 3 Registrational Studies (treatment-naïve HIV-1–infected patients) Administered B/F/TAF STR*



- Mean TAF exposures in HVs (n=202) and HIV-1–infected patients (n=1207) differed by 2–25%
- Mean TAF exposures in males (n=439) and females (n=47) differed by 12–15%
- All other demographic and disease covariates demonstrated minimal-to-no effects on TAF exposure

Conclusions

- Considering the favorable B/F/TAF safety profile and high virologic response rates across the Phase 3 program,⁸ all demographic and disease covariates evaluated were determined to have no clinically relevant impact on BIC or TAF exposure in HIV-1–infected patients
- No dose adjustment of BIC or TAF is necessary for the evaluated patient demographic or disease covariates

References: 1. Biktarvy [package insert]. Foster City, CA: Gilead Sciences, Inc.; Feb 2018. 2. AIDInfo. <https://aidsinfo.nih.gov/news/2044/adult-arv-panel-classifies-bic-taf-ftc-as-recommended-initial-regimen-for-hiv>. 2018; 3. Daar ES, et al. ID Week 2017, abstr LB-4; 4. Gallant J, et al. Lancet 2017;390:2063-72; 5. Kiyoy C, et al. CROI 2018, abstr 500; 6. Molina JM, et al. CROI 2018, oral 1918; 7. Sax PE, et al. Lancet 2017;390:2073-82; 8. Lutz JD, et al. International Workshop on Clinical Pharmacology of Antiviral Therapy 2018, poster 6. Acknowledgments: We extend our thanks to the patients and their families. This study was funded and conducted by Gilead Sciences, Inc.