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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

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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 components[1]
  - B/F/TAF is a Department of Health and Human Services and International Antiviral Society guidelines-recommended initial regimen for most HIV-1–infected patients[2]
  - 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 resistance[3-7]
- 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

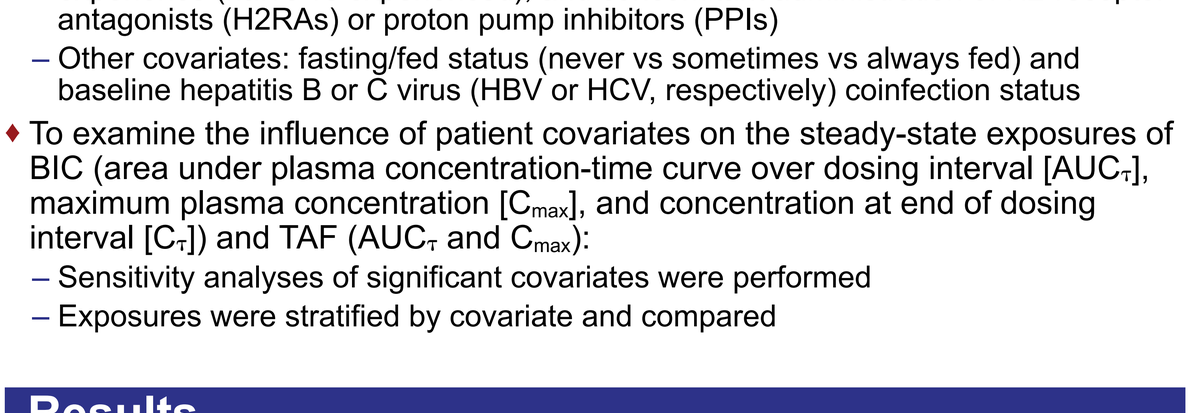
- Significance covariates were determined using a forward addition and backward elimination method (based on significance levels of $p < 0.01$ and $p < 0.001$, respectively)
  - Demographics: baseline age, sex, race (white vs black or African-American vs Asian vs other), body weight (BW), and HIV-1 status (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*

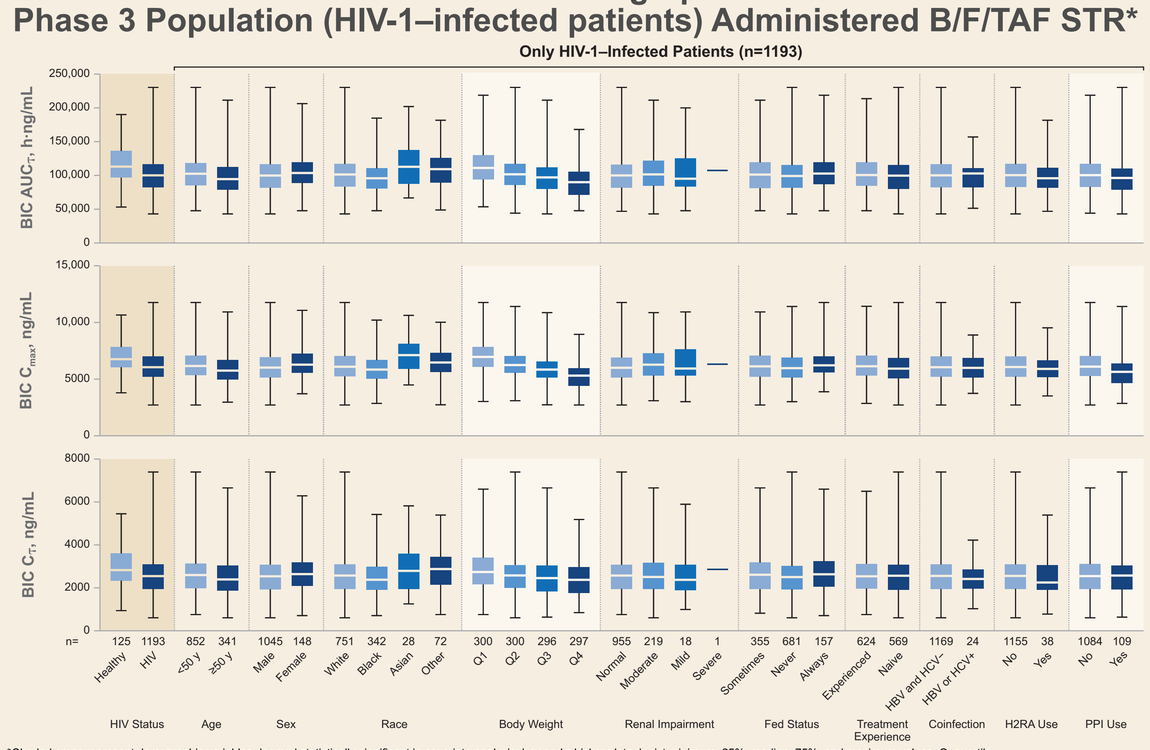


*Base (represented by *black dotted line and values*) refers to predicted steady-state exposure (AUC_τ, C_{max}, or C_τ) of BIC in typical HIV-1–infected patient with BW of 80 kg and no PPI usage; *blue bar with values at each end* shows 5th–95th percentile exposure range across entire population; each *green bar* represents influence of single covariate on steady-state exposure; *label at left end of bar* represents covariate being evaluated; upper and lower values for each covariate capture 90% of plausible range in population; *length of each bar* describes potential impact of that covariate on BIC exposure at steady state, with *% value in parentheses at each end* representing % change of exposure from base; most influential covariate is at *top of plot* for each exposure parameter. CI, confidence interval.

- 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*



Shaded areas represent demographic variables deemed statistically significant in covariate analysis; box and whisker plots depict minimum, 25%, median, 75%, and maximum values. Q, quartile.

- 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

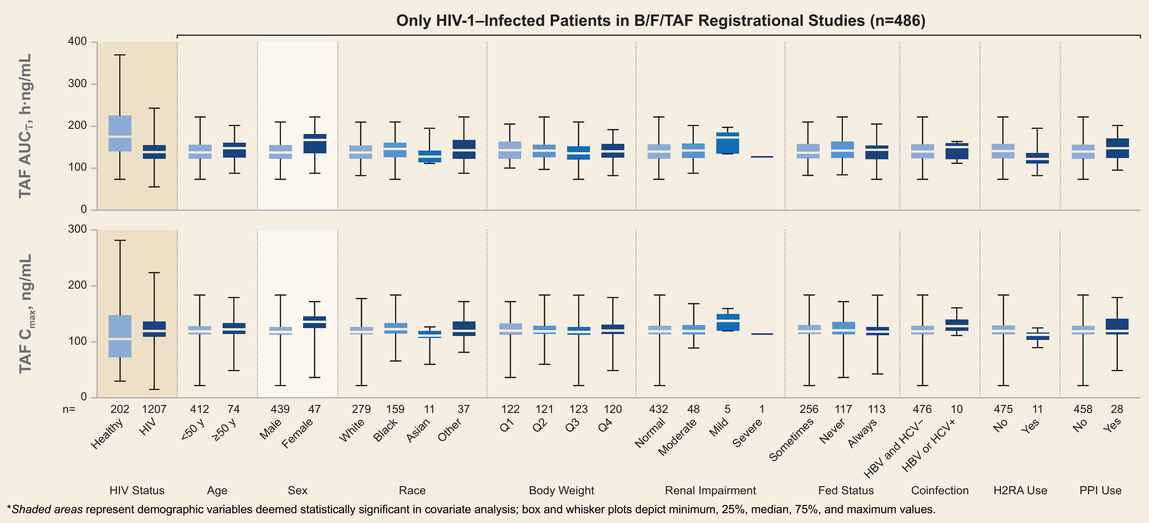
Effect of Covariates on TAF Steady-State Exposure*

*Base (represented by *black dotted line and values*) refers to predicted steady-state exposure (AUC_τ or C_{max}) of TAF in typical male HIV-1–infected patient; *blue bar with values at each end* shows 5th–95th percentile exposure range across entire population; each *green bar* represents influence of covariates on steady-state exposure; *label at left end of bar* represents covariate being evaluated; upper and lower values for each covariate capture 90% of plausible range in population; *length of each bar* describes potential impact of that covariate on TAF exposure at steady state, with *% value in parentheses at each end* representing % change of exposure from base; most influential covariate is at *top of plot* for each exposure parameter.

- 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*



Shaded areas represent demographic variables deemed statistically significant in covariate analysis; box and whisker plots depict minimum, 25%, median, 75%, and maximum values.

- 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.** AIDSinfo. <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.** Kityo C, et al. CROI 2018, abstr 500; **6.** Molina J-M, 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.

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