To access a plain language summary, and supplemental data for this presentation, please scan the QR code

Pharmacokinetics (PK), Safety and Efficacy of Bictegravir/Emtricitabine/Tenofovir Alafenamide (B/F/TAF) in Virologically Suppressed Pregnant Women With HIV

Haeyoung Zhang,[1] Hal Martin,[1] Ludwig Lin,[1] Maggie Davis,[1] Hailin Huang,[1] Deqing Xiao,[1] Priyanka Arora,[1] Anchalee Avihingsanon,[2] Ellen Koenig,[3] Ramesh Palaparthy,[1] Sandhya Girish,[1] Dhananjay Marathe[1]

[1]Gilead Sciences, Inc., Foster City, California, U.S.A.; [2]HIV-NAT Thai Red Cross AIDS Research Centre, Bangkok, Thailand; [3]Dominican Institute of Virological Studies – IDEV, Santiago, Dominican Republic

IAS 2023, the 12th IAS Conference on HIV Science
23–26 July 2023
Brisbane, Australia

All Author Disclosures

- **Dhananjay Marathe (presenting author)**
  - Gilead Sciences: Employment and restricted stocks
- **Haeyoung Zhang, Hal Martin, Ludwig Lin, Maggie Davis, Hailin Huang, Deqing Xiao, Priyanka Arora, Ramesh Palaparthy and Sandhya Girish**
  - Gilead Sciences: Employment and restricted stocks
- **Anchalee Avihingsanon**
  - Gilead Sciences: Speaker honoraria and research grants
  - GSK: Research grants
  - MSD: Research grants
  - Viatris: Speaker honoraria and research grants
  - ViiV Healthcare: Speaker honoraria and research grants
- **Ellen Koenig**
  - Gilead Sciences: Study investigator
- **The potential effects of relevant financial relationship with ineligible company have been mitigated**

Introduction

- Safe, effective and convenient treatment options are needed for pregnant women with HIV
- B/F/TAF is approved for treatment in people with HIV-1 (PWH)
- Limited data exist on B/F/TAF PK, safety and efficacy during pregnancy

- Bictegravir (BIC) is highly protein bound and metabolized by UGT1A1 and CYP3A4
- Increased activities of CYP3A4 and UGT1A1, along with alterations in protein binding and other physiological changes, have been reported in pregnancy

- To evaluate PK, safety and efficacy of B/F/TAF in pregnancy, a dedicated study was conducted
  - Open-label study (NCT03960645) in 33 pregnant women living with HIV-1
  - All participants were virologically suppressed at study start (HIV-1 RNA < 50 c/mL)

Primary Objective:
- Evaluate steady-state PK of BIC and confirm dose of B/F/TAF (50/200/25 mg FDC once daily) in the second and third trimesters of pregnancy

Secondary Objectives:
- Evaluate steady-state PK of FTC and TAF
- Assess maintenance of HIV-1 virologic suppression during the second and/or third trimesters of pregnancy

B/F/TAF, bictegravir/emtricitabine/tenofovir alafenamide; BIC, bictegravir; c, copies; CYP3A4, cytochrome P450 3A4; FDC, fixed-dose combination; FTC, emtricitabine; PK, pharmacokinetics; PWH, people with HIV-1; UGT1A1, uridine diphosphate-glucuronosyltransferase 1A1; TAF, tenofovir alafenamide

Study Design and Sampling Method

Open-label, single-arm, prospective study of 33 pregnant women with HIV-1 who are VS (VL < 50 c/mL)*

Treatment with B/F/TAF (up to ~38 weeks)

Second and Third Trimester

6 and 12 Weeks Postpartum

- Steady-state intensive PK plasma sample collection over 24 hours post-dose (BIC, FTC and TAF)
- Plasma protein binding (BIC and TAF)
- PBMC collection (TFV-DP measurement)†
- Cord blood collection at delivery (BIC and TAF)
- HIV-1 RNA/CD4 cell count
- Safety assessment

Neonates

- Sparse washout PK samples (BIC and TAF)
- HIV-1 RNA and safety assessment

GLSM ratios for PK comparisons between pregnancy and postpartum samples

1

Primary Endpoint

- AUC_{tau} of BIC during second and/or third trimesters through 6 and 12 weeks postpartum

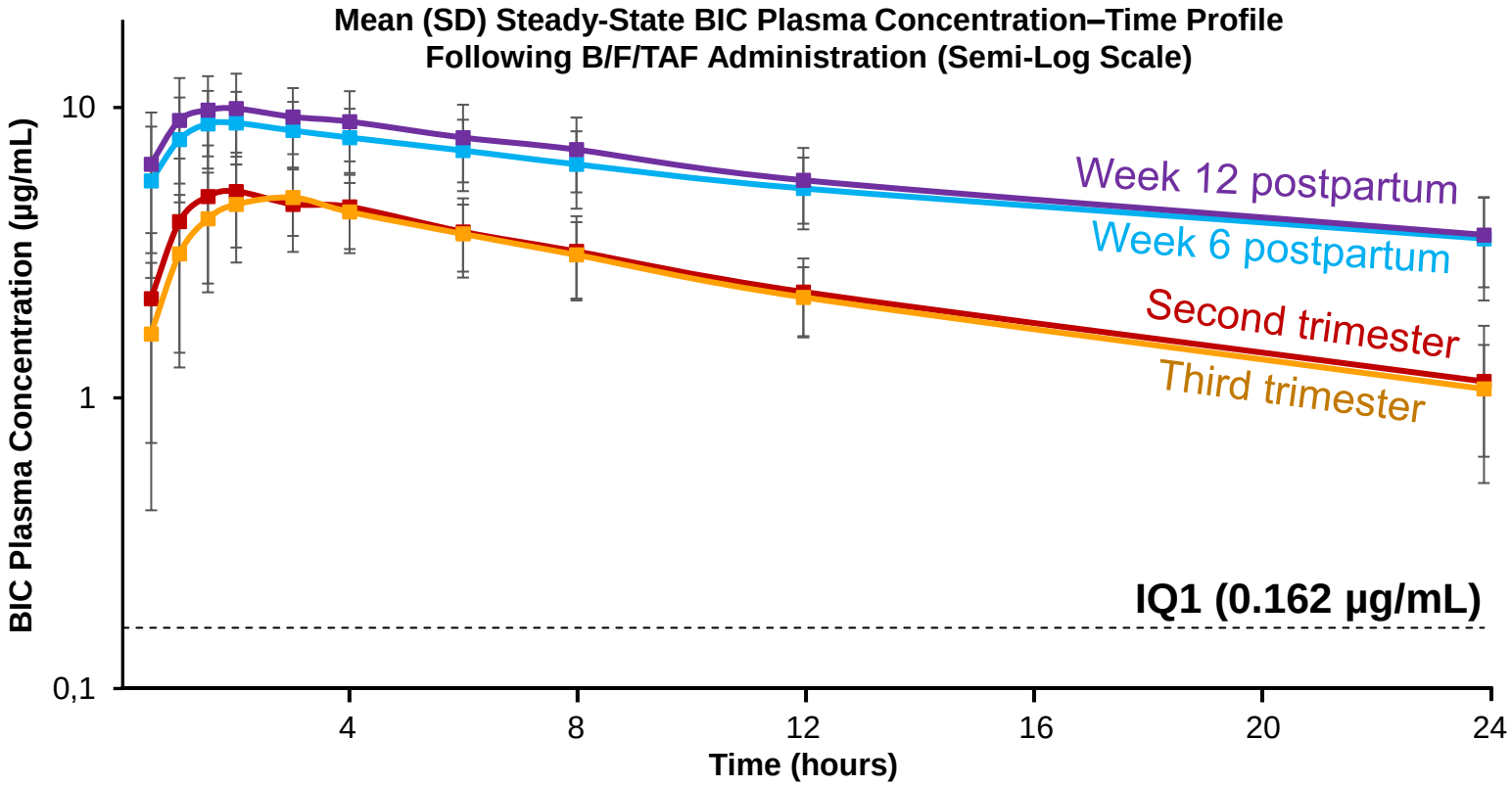
2

Secondary Endpoints

- AUC_{tau} for FTC, TAF
- Other PK parameters (e.g., C_{max}, C_{trough}) for BIC, FTC and TAF
- HIV-1 RNA < 50 c/mL at time of delivery (M = E)

*Study inclusion criteria: aged ≥ 18 to < 40 years, documented VL < 50 c/mL for ≥ 6 months, on stable ART for ≥ 6 months, no documented or suspected resistance to any component of FTC, TFV or INSTIs, GFR ≥ 90 mL/min;
†Exploratory endpoint. ART, antiretroviral therapy; AUC_{tau}, area under the plasma drug concentration versus time curve over the dosing interval; B/F/TAF, bictegravir/emtricitabine/tenofovir alafenamide; BIC, bictegravir; c, copies; C_{max}, maximum observed plasma drug concentration; C_{trough}, trough concentration; FTC, emtricitabine; GFR, glomerular filtration rate; GLSM, geometric least-squares mean; INSTI, integrase strand transfer inhibitor; M = E, missing = excluded; PBMC, peripheral blood mononuclear cell; PK, pharmacokinetic; TAF, tenofovir alafenamide; TFV, tenofovir; TFV-DP, tenofovir diphosphate (active metabolite); VL, viral load; VS, virologically suppressed

Pharmacokinetics of BIC: Plasma Concentration–Time Profiles



- **Concentrations were lower during pregnancy vs. postpartum, but similar within each period (second vs. third trimester; 6 vs. 12 weeks)**
- **Individual C_{trough} values were > IQ1 in all participants across each of the four periods except in one participant* during the second trimester (who remained virologically suppressed) ; median C_{trough} was 6.9- and 6.0-fold of IQ1 during the second and third trimesters, respectively**

*Participant on calcium and iron supplements, FTC and TAF exposures in typical population range (> median) at second trimester; the same participant had > 9-fold BIC exposure in third vs. second trimester (i.e., ~ 4.8-fold IQ1).
B/F/TAF, bictegravir/emtricitabine/tenofovir alafenamide; BIC, bictegravir; C_{trough}, trough concentration; FTC, emtricitabine; IQ1, inhibitory quotient at protein-adjusted 95% effective concentration; SD, standard deviation; TAF, tenofovir alafenamide

Pharmacokinetics of BIC

Parameter Mean (%CV)	Second trimester (n = 21)	**Third trimester (n = 30)**	Week 6 postpartum (n = 31)	**Week 12 postpartum (n = 32)**	**Third trimester vs. Week 12 postpartum (%GLSM ratio [90% CI])**
Total AUC_{tau}, h•µg/mL	62.8 (32.2)	60.2 (29.1)	135 (26.9)	148 (28.5)	40.6 (36.8, 44.8)
Unbound AUC_{tau}, h•µg/mL	0.224 (42.0)	0.219 (33.9)	0.354 (34.2)	0.374 (32.2)	58.8 (52.7, 65.7)
C_{max}, µg/mL	5.82 (30.1)	5.37 (25.9)	9.77 (23.3)	11.0 (24.9)	48.2 (43.0, 53.9)
C_{trough}, µg/mL	1.05 (45.2)	1.07 (41.7)	3.53 (38.4)	3.64 (34.1)	29.0 (25.7, 32.7)

- **Compared with 12 weeks postpartum, total and unbound BIC AUC_{tau} during the third trimester were lower by ~59% and ~41%, respectively**
- **In concordance with the current study data, IMPAACT data presented at CROI 2023 showed that total BIC exposure was lower in pregnancy vs. postpartum, while all BIC C_{trough} values were > IQ1[1]**

%CV, percentage coefficient of variation; AUC_{tau}, area under the plasma drug concentration versus time curve over the dosing interval; BIC, bictegravir; C_{max}, maximum observed plasma concentration of drug; C_{trough}, trough concentration; GLSM, geometric least-squares mean; IQ1, inhibitory quotient at protein-adjusted 95% effective concentration

1. Powis KM, et al. CROI 2023, Poster 783. Pharmacokinetics And Virologic Outcomes Of Bictegravir In Pregnancy And Postpartum - CROI Conference (accessed June 22, 2023)

Pharmacokinetics of BIC

Parameter Mean (%CV)	Second trimester (n = 21)	Third trimester (n = 30)	Week 6 postpartum (n = 31)	Week 12 postpartum (n = 32)	Non-pregnant adult PWH (n = 1193)[1,2]
Total AUC_{tau}, h•µg/mL	62.8 (32.2)	60.2 (29.1)	135 (26.9)	148 (28.5)	102 (26.9)
Unbound AUC_{tau}, h•µg/mL	0.224 (42.0)	0.219 (33.9)	0.354 (34.2)	0.374 (32.2)	–
C_{max}, µg/mL	5.82 (30.1)	5.37 (25.9)	9.77 (23.3)	11.0 (24.9)	6.15 (22.9)
C_{trough}, µg/mL	1.05 (45.2)	1.07 (41.7)	3.53 (38.4)	3.64 (34.1)	2.61 (35.2)

- **Exposure levels in pregnancy are closer to those in non-pregnant adult PWH**
  - **Mean total BIC AUC_{tau} in the third trimester was ~41% lower than values reported in non-pregnant adult PWH[1]**

%CV, percentage coefficient of variation; AUC_{tau}, area under the plasma drug concentration versus time curve over the dosing interval; BIC, bictegravir; C_{max}, maximum observed plasma concentration of drug; C_{trough}, trough concentration; IQ1, inhibitory quotient at protein-adjusted 95% effective concentration; PWH, people with HIV-1

1. Biktarvy USPI. https://www.gilead.com/-/media/files/pdfs/medicines/hiv/biktarvy/biktarvy_pi.pdf (accessed June 13, 2023); 2. FDA Biktarvy Uni-Review. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/210251Orig1s000MultidisciplineR.pdf (accessed June 22, 2023)

Pharmacokinetics of FTC and TAF

- Plasma FTC exposures were lower during pregnancy compared with postpartum; %GLSM ratio for AUC_{tau} ranged from 64.3% to 69.2%
- Plasma TAF exposures were lower during pregnancy compared with postpartum; %GLSM ratio for total AUC_{tau} ranged from 56.5% to 77.6%
  - When adjusted for changes in protein binding, %GLSM ratio for unbound AUC_{tau} ranged from 83.6% to 89.3%
- Trough TFV-DP levels in PBMCs were generally similar (but variable) during pregnancy and postpartum period
- In other published literature, there were changes of similar magnitude in FTC and TAF exposure during pregnancy, and these were not associated with virologic failure or perinatal (vertical) transmission[1,2]
- U.S. DHHS clinical guidelines state that no dose adjustments are required for FTC or TAF during pregnancy[3]

AUC_{tau}, area under the plasma drug concentration versus time curve over the dosing interval; DHHS, Department of Health and Human Services; FTC, emtricitabine; GLSM, geometric least-squares mean; PBMC, peripheral blood mononuclear cell; TAF, tenofovir alafenamide; TFV-DP, tenofovir diphosphate

1.Colbers APH, et al. AIDS 2013;27:739-748; 2. Brooks KM, et al. AIDS 2021;35:407-417; 3. DHHS. https://clinicalinfo.hiv.gov/en/guidelines/perinatal/whats-new (accessed June 13, 2023)

Neonatal PK for BIC

BIC

- Mean (%CV) cord blood to maternal blood plasma concentration ratio (n = 29): **1.4 (35%)**
- Median $t_{½}$ in neonates (n = 10): **43.1 hours**
- Other neonatal BIC PK parameters were not calculable or meaningful

BIC $t_{½}$ **in neonates** (43 hours) was longer than that in adults (~18 hours across postpartum)

%CV, percentage coefficient of variation; BIC, bictegravir; PK, pharmacokinetic(s); $t_{1/2}$, terminal elimination half-life

All Participants Were Virologically Suppressed at Delivery and Up to 18 Weeks Postpartum

Virologic Suppression in Adults

- **Virologic suppression was maintained during pregnancy, delivery and through Week 18 postpartum**
- **All (100%) adult participants had HIV-1 RNA < 50 c/mL at delivery (32/32) and through Week 18 postpartum (32/32)***
- **No virologic failure or treatment-emergent resistance was observed**

CD4 Cell Count and CD4% in Adults

- CD4 cell count at baseline median (Q1, Q3): **558 (409, 720) cells/μL**
- Change from baseline to Week 12 postpartum, median (Q1, Q3): **159 (27, 296) cells/μL**
- CD4% at baseline, median (Q1, Q3): **32.3% (27.0%, 40.2%)**
- Change from baseline at Week 12 postpartum, median (Q1, Q3): **0.1% (-2.3%, 4.2%)**

No Virologic Findings in Neonates

- **29/29 of enrolled neonates were HIV PCR negative**

- **In concordance with the current study data, IMPAACT data presented at CROI 2023 reported that 90% of participants receiving B/F/TAF during pregnancy were virologically suppressed at delivery†[1]**
- **Additionally, in IMPAACT, no infant was confirmed to have acquired HIV[1]**

*Prespecified efficacy analysis using M = E, includes 32 participants with available data (1 participant prematurely discontinued from the study due to a protocol violation); †In IMPAACT one participant had a viral load > 200 c/mL.
B/F/TAF, bictegravir/emtricitabine/tenofovir alafenamide; c, copies; M = E, missing = excluded; PCR, polymerase chain reaction; Q, quartile. 1. Powis KM, et al. CROI 2023, Poster 783

B/F/TAF Was Generally Well Tolerated in Adults and Neonates

	Maternal (N = 33*)	Neonate (N = 29)
Type of AE n (%)		
Any AE	26 (79)	12 (41)
Common AEs	Back pain 4 (12) Gestational diabetes 4 (12) Anemia 3 (9) False labor 3 (9) Preeclampsia 3 (9)	Neonatal jaundice 3 (10) Respiratory distress 3 (10)
Drug-related AE	1 (3)†	0
SAE	6 (18)	5 (17)
Drug-related SAE	1 (3)†	0
AE leading to premature discontinuation	0	0
Death	0	0
Laboratory evaluations		
Grade 1/2 Grade ≥ 3	24 (72) 6 (18)	5 (17) 0

All laboratory-related AEs were Grade 1

Majority of AEs were Grade 1/2; Grade ≥ 3 AE reported in 1 (3%) neonate (neonatal asphyxia)

Majority were Grade 1/2; Grade ≥ 3 reported in 2 (6%) participants (gestational diabetes and pyrexia)

One drug-related AE (false labor) was reported; this was an SAE

Grade 3 laboratory AEs of hematuria (5 [15%]) and glycosuria (1 [3%])‡

There were no discontinuations due to AEs

Median duration of B/F/TAF exposure was 27 weeks

*Enrolled participants treated with B/F/TAF; †False labor; ‡Grade 3 glycosuria in a hyperglycemic participant with gestational diabetes

AE, adverse event; B/F/TAF, bictegravir/emtricitabine/tenofovir alafenamide; SAE, serious adverse event

Conclusions

- BIC exposure was lowered during pregnancy; exposure difference was lesser in comparison with non-pregnant adult PWH[1]
- All individual BIC C_{trough} values were > IQ1, except in one participant during the second trimester; median C_{trough} was ~6- to 7- fold higher than IQ1 during pregnancy
- FTC and TAF PK observations were consistent with published literature[2,3]

- All (32/32) adult participants had HIV-1 RNA < 50 c/mL at delivery and maintained virologic suppression through 18 weeks postpartum, with no observed virologic failure or treatment-emergent resistance
- Median CD4 cell count and CD4% remained stable for adult participants through postpartum
- No cases of perinatal HIV-1 transmission

- B/F/TAF was well tolerated in pregnant women through their second and third trimesters and postpartum
- No discontinuations due to AEs
- AEs were mostly Grade 1/2; overall incidence and types of AE were consistent with those expected

Data from this study and available evidence suggest the suitability of once-daily B/F/TAF use throughout pregnancy, including the second and third trimesters, and indicate that no dose change is needed[2-5]

AE, adverse event; B/F/TAF, bictegravir/emtricitabine/tenofovir alafenamide; BIC, bictegravir; c, copies; C_{trough}, trough concentration; IQ1, inhibitory quotient at protein-adjusted 95% effective concentration; PWH, people with HIV-1

1. Biktarvy USPI. https://www.gilead.com/-/media/files/pdfs/medicines/hiv/biktarvy/biktarvy_pi.pdf (accessed June 13, 2023); 2.Colbers APH, et al. AIDS 2013;27:739-748; 3. Brooks KM, et al. AIDS 2021;35:407-417;
4. DHHS. https://clinicalinfo.hiv.gov/en/guidelines/perinatal/whats-new (accessed June 13, 2023); 5. Powis KM, et al. CROI 2023, Poster 783

Acknowledgments

To access a plain language summary, and supplemental data for this presentation, please scan the QR code

Thank you to the investigators, study staff and all participants

This study was funded by Gilead Sciences (NCT03960645). Medical writing support was provided by Olivia Morris, PhD, of Aspire Scientific Ltd (U.K.) and was funded by Gilead Sciences.
The authors thank Jason Hindman (Gilead Sciences) for valuable contributions to this oral presentation.