# Sustained Viral Suppression among Participants with Pre-existing M184V/I Who Switched to Bictegravir/Emtricitabine/Tenofovir Alafenamide

Poster 5162
CONFERENCE CAHR 2020

**Kristen Andreatta[1], Benoit Trottier[2], Rima Acosta[1], Michelle D'Antoni[1], Danielle Porter[1], Silvia Chang[1], Ross Martin[1], Madeleine Willkom[1], Ian McNicholl[1], Joel Gallant[1], Cheryl Pikkora[1], Hiba Graham[1], Sean Collins[1], Hal Martin[1], Kirsten White[1]**

[1]Gilead Sciences, Inc., Foster City, LA, USA, [2]Clinique de médecine urbaine du Quartier Latin, Montreal, QC, Canada

GILEAD
Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404
Tel: (650) 574-3000
Fax: (650) 578-9264

## Introduction

- M184V/I is a common NRTI resistance substitution
  - Confers high-level resistance to 3TC and FTC and decreases susceptibility to ABC and ddI, but increases susceptibility to tenofovir (TFV) and AZT[1]
  - Occurs in up to 67% of patients after treatment failure[2]
  - Recently, Monogram Biosciences reported the detection of M184V/I in 27% of HIV-1 DNA samples by the GenoSure Archive assay, which was the most frequently observed resistance substitution among >64,000 patient samples[3]
- However, M184V/I prevalence may be under-reported and M184V/I is often under-recognized in standard clinical practice
  - Detected in up to 23% of primary infections, but rarely detected in chronically infected, treatment-naïve people with HIV (PWH) suggesting high transmission frequency with rapid reversion to wild-type in circulating viruses, but with mutant virus archived in the latent reservoir[2]
  - In virologically suppressed PWH, only ~50% of previously documented M184V/I is detected by proviral DNA genotyping using next generation sequencing, including the GenoSure Archive assay[4,5] and the deepType HIV assay when mutation detection cutoff is ≥15% of deep sequence reads[6]
- B/F/TAF (bictegravir/emtricitabine/tenofovir alafenamide) is an EACS, IAS-USA, and DHHS guidelines-recommended regimen for the treatment of HIV-1 infection[7-9]
- B/F/TAF safety and efficacy has been demonstrated in controlled clinical trials through 144 weeks[10-16]
  - No treatment-emergent resistance to B/F/TAF has been detected in clinical trial participants, including those with pre-existing NRTI resistance10-19
- Several studies demonstrated that triple therapy regimens containing FTC and TFV in either prodrug form (TDF or TAF) are able to maintain high rates of virologic suppression in the presence of archived M184V/I[4,20-21]

## Objectives

- To determine:
  - The prevalence of, and risk factors for, pre-existing M184V/I among virologically suppressed clinical trial participants
  - The impact of pre-existing M184V/I on virologic outcomes after switching to B/F/TAF

## Methods

### Table 1. Overview of B/F/TAF Switch Studies in Virologically Suppressed People with HIV

| Study | Resistance Criteria | M184V/I at Screening | Population Age | Prior ARV Regimen | Number of Participants | Study Phase and Treatment: Randomized Phase |
|---|---|---|---|---|---|---|
| 4030 | NRTI, NNRTI, PI resistance allowed, INSTI resistance excluded | Allowed | Adults ≥18 years old | DTG + either F/TAF or F/TDF | 284 | B/F/TAF (DTG + F/TAF placebo) |
| | | | | | 281 | DTG + F/TAF (B/F/TAF placebo) |
| 1844 | FTC or TFV resistance excluded | Excluded | Adults ≥18 years old | DTG + ABC/3TC | 282 | B/F/TAF (DTG/ABC/3TC placebo) |
| | | | | | 281 | DTG/ABC/3TC (B/F/TAF placebo) |
| 1878 | FTC or TFV resistance excluded | Excluded | Adults ≥18 years old | Boosted DRV or ATV + either F/TDF or ABC/3TC | 290 | B/F/TAF |
| | | | | | 287 | Stay on baseline regimen |
| 4449 | FTC, TFV, and BIC resistance excluded | Excluded | Adults ≥65 years old | E/C/F/TAF or Any 3rd Agent + F/TDF | 86 | B/F/TAF |
| 1474 | FTC, TFV, and INSTI resistance excluded | Excluded | Adolescents & children 6 to <18 years old | Any 3rd Agent + 2 NRTIs | 100 | B/F/TAF |

### Baseline Genotypic Analyses

- Historical HIV-1 genotype reports were collected if available upon enrollment
- HIV-1 proviral DNA genotype testing (GenoSure Archive, Monogram Biosciences) was performed on baseline samples
  - Bioinformatics filters removed APOBEC-mediated hypermutated deep sequence reads from GenoSure Archive results to prevent over-reporting of E138K, M184I, and M230I in RT and G163R in IN
- Participants with pre-existing resistance detected after enrollment continued on study and were included in all analyses

### Resistance Analysis Population (RAP)

- Resistance testing was performed in participants with HIV-1 RNA ≥200 c/mL at confirmed virologic failure, Week 48, or last visit on study drugs
- Plasma HIV-1 RNA genotype and phenotype (PhenoSenseGT, GeneSeq IN, and PhenoSense IN, Monogram Biosciences)

### HIV-1 Drug Resistance Substitutions (based on IAS-USA)[12]

- **NRTI-R:** K65R/E/N, T69 insertions, K70E, L74V/I, Y115F, Q151M, M184V/I, TAMs (M41L, D67N, K70R, L210W, T215F/Y, K219E/N/Q/R)
- **NNRTI-R:** L100I, K101E/P, K103N/S, V106A/M, V108I, E138A/G/K/Q/R, V179L, Y181C/I/V, Y188C/H/L, G190A/E/Q/S, H221Y, P225H, F227C, M230I/L; rilpvirine resistance substitutions (RPV-R): L100I, K101E/P, E138A/G/K/Q/R, V179L, Y181C/I/V, Y188L, H221Y, F227C, M230I/L
- **PI-R:** D30N, V32I, M46I/L, I47A/V, G48V, I50L/V, I54M/L, Q58E, T74P, L76V, V82A/F/L/S/T, N83D, I84V, N88S, L90M
- **INSTI-R:** T66I/A/K, E92Q/G, T97A, F121Y, Y143R/H/C, S147G, Q148H/K/R, N155H/S, R263K

### Efficacy Analyses

- Analyses included participants who switched to B/F/TAF and had ≥1 on-study HIV-1 RNA measurement
- Virologic outcomes based on last available on-treatment HIV-1 RNA using last observation carried forward (LOCF) imputation: <50 c/mL (success) or ≥50 c/mL (failure)
  - All participants with data, including those with early discontinuation, had virologic outcomes determined

### Statistical Analyses

- We assessed risk factors for M184V/I using a multivariate logistic regression model with stepwise selection significance level for entry (SLE) α = 0.20 and significance level for stay (SLS) α = 0.05 and adjusted for study specific effects
  - **Analysis included:** all participants from the B/F/TAF and comparator treatment groups with baseline genotypic data from Studies 4030 (n=470), 1844 (n=528), and 1878 (n=524)
    - Participants from Studies 4449 and 1474 were excluded due to possible confounding effects of study age requirements
  - **Intrinsic predictors:** groups of age, sex, race, ethnicity, BMI, CKD stage, region
  - **HIV specific variables at baseline:** CD4, HIV RNA, HIV acquisition risk factor, HIV disease status, time since ART start, prior treatment with any PI, NNRTI, INSTI, or non-DTG INSTI (RAL or EVG), number of prior 3rd agents, number of prior 3rd agent classes, duration of baseline ARV regimen
  - **HIV resistance variables:** non-M184V/I primary NRTI-R, TAMs, primary PI-R, primary NNRTI-R, RPV-R, primary and secondary INSTI-R

3TC = lamivudine; ABC = abacavir; ART = antiretroviral therapy, ARV = antiretroviral, ATV = atazanavir; BMI = body mass index, C = cobicistat; CKD = chronic kidney disease, DRV = darunavir; DTG = dolutegravir, EVG or E = elvitegravir, FTC or F = emtricitabine; INSTI = integrase strand transfer inhibitor, NNRTI = nonnucleoside reverse transcriptase inhibitor, NRTI = nucleos(t)ide reverse transcriptase inhibitor, PI = protease inhibitor, -R = resistance, RAL = raltegravir, RPV = rilpivirine, TAF = tenofovir alafenamide; TAMs = thymidine analog mutations; TDF = tenofovir disoproxil fumarate; TFV = tenofovir

## Results

### Section 1. Studies 4030, 1844, 1878, 4449, and 1474 (B/F/TAF Groups)

### Table 2. Virologic Outcomes of Participants Switched to B/F/TAF

| | Pooled B/F/TAF | B/F/TAF Group by Study | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | Study 4030 | Study 1844 | | Study 1878 | | Study 4449 | Study 1474 |
| | | | Group 1a | Group 2b | Group 1a | Group 2b | | |
| Number of Participants Analyzed, n | 1545 | 283 | 281 | 264 | 289 | 243 | 85 | 100 |
| Analysis Time point | – | Week 48 | OLE Median Week 117 | OLE Median Week 50 | OLE Median Week 116 | OLE Median Week 71 | Week 48 | Week 24 or Week 48[c] |
| HIV-1 RNA <50 c/mL, % (n) | 98.9% (1528) | 99.6% (282) | 98.2% (276) | 98.9% (261) | 98.6% (285) | 98.8% (240) | 100% (85) | 99.0% (99) |
| HIV-1 RNA ≥50 c/mL, % (n) | 1.1% (17) | 0.4% (1) | 1.8% (5) | 1.1% (3) | 1.4% (4) | 1.2% (3) | 0 | 1.0% (1) |
| Emergent Resistance, n | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

Group 1 participants switched to B/F/TAF on Day 1 of study randomized phase
Group 2 participants continued baseline regimen during randomized phase and switched to B/F/TAF in open-label extension (OLE)
75 participants completed 48 weeks of B/F/TAF treatment and 25 participants completed 24 weeks of B/F/TAF treatment

- B/F/TAF maintained high rates of virologic suppression with no treatment-emergent resistance

### Table 3. Frequency of Baseline Resistance-Associated Substitutions in the Pooled B/F/TAF Treatment Group

| | Proportion of Participants, % (n or n/N) |
|---|---|
| **Baseline Genotype** | **Pooled B/F/TAF (n=1545)** |
| PR/RT Data Available (Historical and/or Proviral) | 88% (1356) |
| **NRTI-R** | **16% (220/1356)** |
| M184V/I | 9.7% (132) |
| V only substitution | 8.6% (116) |
| I only substitution | 0.7% (10) |
| V and I substitutions | 0.4% (6) |
| **K65R/E/N** | **1.0% (14)** |
| **Any TAM** | **9.7% (132)** |
| **NNRTI-R** | **22% (295/1356)** |
| RPV-R | 10% (135) |
| K103N/S | 11% (152) |
| **PI-R** | **10% (135/1356)** |
| IN Data Available (Historical and/or Proviral) | 83% (1278) |
| INSTI-R | 3.7% (47/1278) |
| T97A | 2.2% (28) |

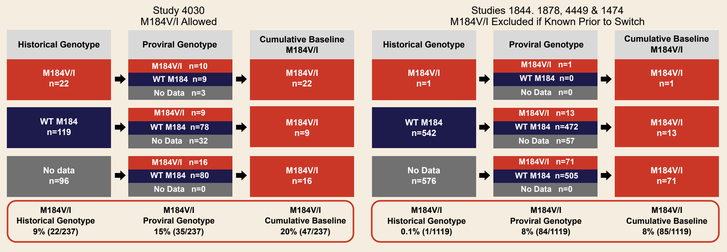
### Table 4. Frequency of Pre-existing M184V/I by Study

| | Proportion of Participants, % (n or n/N) | | | | | | |
|---|---|---|---|---|---|---|---|
| | Study 4030 (n=283) | Study 1844 | | Study 1878 | | Study 4449 (n=85) | Study 1474 (n=100) |
| **Baseline Genotype** | | Group 1 (n=281) | Group 2 (n=264) | Group 1 (n=289) | Group 2 (n=243) | | |
| **RT Data Available[a]** | **84% (237)** | **95% (267)** | **97% (255)** | **96% (276)** | **91% (222)** | **96% (82)** | **17% (17)** |
| M184V/I | 20% (47/237) | 3.7% (10/267) | 2.7% (7/255) | 16% (44/276) | 8.1% (18/222) | 3.7% (3/82) | 18% (3/17) |
| V only substitution | 18% (43) | 2.6% (7) | 2.4% (6) | 19% (39) | 6.8% (15) | 3.7% (3) | 18% (3) |
| I only substitution | 0.8% (2) | 0.7% (2) | 0.4% (1) | 1.4% (3) | 0.9% (2) | 0 | 0 |
| V and I substitutions | 0.8% (2) | 0.5% (1) | 0 | 1.0% (2) | 0.5% (1) | 0 | 0 |

[a]From cumulative historical and/or proviral genotypes

- M184V/I was detected in 132 suppressed participants enrolled across 5 studies, including 85 that would have been excluded if known prior to randomization

### Figure 1. M184V/I Detection by Historical and Baseline Proviral Genotypes




- Pre-existing M184V/I was detected in 10% (132/1356) of participants switched to B/F/TAF
  - Most M184V/I was identified by baseline proviral DNA genotyping

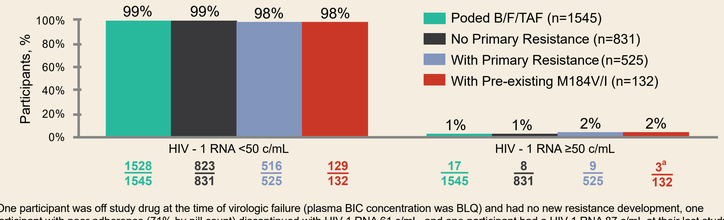
### Table 5. Association of M184V/I with Other Resistance Substitutions

| | Proportion of Participants, % (n/N) | |
|---|---|---|
| | Pooled B/F/TAF With Pre-existing M184V/I (n=132) | HIV-1 RNA <50 c/mL at Last Visit |
| M184V/I alone | 23% (31/132) | 97% (30/31) |
| M184V/I + ≥1 primary resistance substitution | 77% (101/132) | 98% (99/101) |
| M184V/I + NNRTI-R | 52% (68/132) | 99% (67/68) |
| M184V/I + Other NRTI-R | 47% (62/132) | 98% (61/62) |
| M184V/I + TAMs | 40% (53/132) | 98% (52/53) |
| M184V/I + PI-R | 20% (27/132) | 100% (27/27) |
| M184V/I + Primary INSTI-R | 4% (5/132)[a] | 100% (5/5) |

[a]Primary INSTI-R substitutions observed with M184V/I: T97A (n=2) and Y143H, Q148R, and N155H (n=1 each).

- M184V/I was frequently detected with other primary resistance substitutions, but was the only resistance substitution detected in 23% of participants

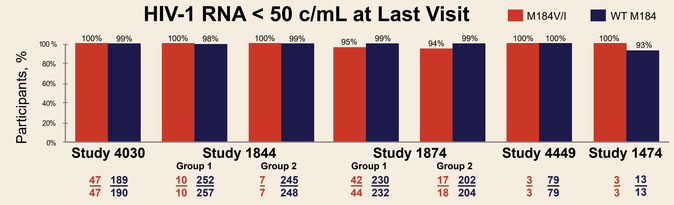
### Figure 2. Virologic Outcomes by Pre-existing Resistance, Pooled B/F/TAF Analysis




[a]One participant was off study drug at the time of virologic failure (plasma BIC concentration was BLQ) and had no new resistance development, one participant with poor adherence (71% by pill count) discontinued with HIV-1 RNA 61 c/mL, and one participant had a HIV-1 RNA 87 c/mL at their last study visit then switched to commercial B/F/TAF and resuppressed at their follow-up visit

- B/F/TAF efficacy was not affected by resistance at baseline

### Figure 3. Virologic Suppression at Last On-treatment Visit Stratified by Study and Pre-existing M184V/I (n=132)




One participant was off study drug at the time of virologic failure (plasma BIC concentration was BLQ) and had no new resistance development, one participant with poor adherence (71% by pill count) discontinued with HIV-1 RNA 61 c/mL, and one participant had a HIV-1 RNA 87 c/mL at their last study visit then switched to commercial B/F/TAF and resuppressed at their follow-up visit

- No difference in the rates of virologic suppression between participants with or without pre-existing M184V/I

### Section 2. Studies 4030, 1844, and 1878 (All Treatment Groups)

### Table 6. Baseline Characteristics Stratified by M184V/I Detection in Studies of Suppressed Adults

| | Participants with Baseline Data Pooled Studies 1844, 1878, & 4030 | |
|---|---|---|
| | M184V/I (n=162) | Wild-type M184 (n=1360) |
| Race/Ethnicity, % (n) | | |
| Non-Black | 64% (101) | 78% (1058) |
| Black or African American | 36% (58) | 22% (299) |
| Hispanic/Latino | 25% (39) | 17% (237) |
| Mean time since ART start, years (range) | 16.2 (0.8–32.2) | 8.5 (0.3–31.8) |
| Mean CD4 count, cells/µL (range) | 633 (173–1515) | 697 (18–2582) |
| CD4 <500 cells/µL , % (n) | 36% (59) | 27% (370) |
| CD4 ≥500 cells/µL, % (n) | 64% (103) | 73% (990) |
| HIV status, % (n) | | |
| Symptomatic or AIDS | 25% (40) | 16% (217) |
| Asymptomatic | 75% (122) | 84% (1143) |
| Resistance substitutions present, % (n) | | |
| NRTI-R (other than M184V/I) | 48% (77) | 8% (107) |
| NNRTI-R | 51% (83) | 19% (263) |
| PI-R | 20% (33) | 8% (113) |

### Table 7. Risk Factors Associated with Pre-existing M184V/I by Multivariate Logistic Regression Model

| Variables Associated with Pre-existing M184V/I | OR (95% CI) | p-value |
|---|---|---|
| Black race (vs non-Black) | 2.57 (1.67, 3.97) | < 0.001 |
| Hispanic/Latino ethnicity (vs not Hispanic/Latino) | 1.84 (1.13, 3.00) | 0.014 |
| Time since ART start (per year) | 1.09 (1.06, 1.12) | < 0.001 |
| CD4 <500 cells/µL (vs ≥500 cells/µL) | 1.57 (1.03, 2.40) | 0.035 |
| HIV status: symptomatic or AIDS (vs asymptomatic) | 1.74 (1.08, 2.82) | 0.024 |
| History of NRTI resistance (other than M184V/I) | 4.56 (2.87, 7.25) | < 0.001 |
| History of NNRTI resistance | 2.80 (1.87, 4.19) | < 0.001 |
| History of PI resistance | 1.86 (1.07, 3.25) | 0.029 |

The results are adjusted by study effect

- Risk factors associated with M184V/I include Black race, Hispanic/Latino ethnicity, longer time since ART treatment started (10% per year), CD4 cell count <500 cells/µL, symptomatic HIV status or AIDS, and NRTI-R (other than M184V/I), NNRTI-R, or PI-R

## Conclusions

- Virologically suppressed participants who switched to B/F/TAF in Studies 1844, 1878, 4030, 4449, and 1474 maintained viral suppression with no treatment emergent resistance
  - 99% had HIV-1 RNA <50 c/mL at their last study visit
- M184V/I was detected in 132/1356 (10%) of participants, most of which was previously undocumented
- High efficacy was observed among participants with pre-existing M184V/I who switched to B/F/TAF
  - 98% with M184V/I an had HIV-1 RNA <50 c/mL at their last study visit
  - No treatment-emergent resistance was detected
- M184V/I at baseline was associated with Black race, Hispanic/Latino ethnicity, a longer duration of ART, CD4 cell count <500 cells/µL, symptomatic HIV or AIDS, and other NRTI, NNRTI, or PI resistance
- A triple therapy regimen of B/F/TAF is an effective treatment option for suppressed PLWH, including those with known or unidentified M184V/I

## References & Acknowledgments

1. Miller MD, et al., Antivir Ther (2012) 17: 993-9,
2. Wainberg, MA et al., JAC (2011) 66: 2346-49,
3. Yang, D et al., CROI (2019) Poster #543,
4. Perez-Valero, I et al., IAS (2018), Presentation #TUAB0104,
5. Acosta R, et al., CROI (2019) Poster #551,
6. Thielen A, European Meeting on HIV & Hepatitis (2018) Presentation #5,
7. European AIDS Clinical Society Guidelines Version 9.1, October 2018,
8. Saag MS, et al., JAMA (2018) 320: 379-96,
9. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV, DHHS, http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf,
10. Orkin C, et al., EACS (2019) Poster #PE3/14,
11. Daar ES, et al., The Lancet HIV (2018) 5(7): e347-56,
12. Molina JM, et al., The Lancet HIV (2018) 5(7): e357-65,
13. Kityo C, et al., IAS (2019) Presentation #MOAB0106,
14. Sax PE, et al., IAS (2019) Presentation #MOAB0105,
15. Maggiolo F, et al., EACS (2019) Poster # PE9/49,
16. Gaur AH, et al., CROI (2019) Presentation #46,
17. Acosta R, et al., IAS (2019) Poster #MOPEB242,
18. Andreatta K, et al., CROI (2019) Poster #552,
19. Andreatta K, et al., IAS (2019) Presentation #,
20. Lathouwers E, et al., HIV Glasgow (2018), Poster #P294,
21. Andreatta K, et al., JAIDS (2018) 79: e47-50.
22. Wensing AM, et al., Top Antivir Med (2017) 24: 132-41.

We extend our thanks to the participants and their families, study investigators and staff.
For information regarding this poster, contact Kristen Andreatta: Kristen.Andreatta@gilead.com

## Disclosures

Kristen Andreatta is an employee of Gilead Sciences and Dr. Beniot Trottier has received honorarium for consultation from Gilead, Merck, ViiV Healthcare and sponsorship to attend international conference from Gilead. These studies were funded by Gilead Sciences, Inc.

**Presented at the 29th Annual Canadian Conference on HIV/AIDS Research (CAHR), April 30 - May 3, 2020, Quebec City, Quebec, Canada**