P298

High Prevalence of Previously Undocumented Baseline M184V/I Does Not Affect Virologic Outcome in Virologically-Suppressed Patients Switching to Bictegravir/Emtricitabine/Tenofovir Alafenamide (B/F/TAF) from a Boosted Protease Inhibitor-based Regimen

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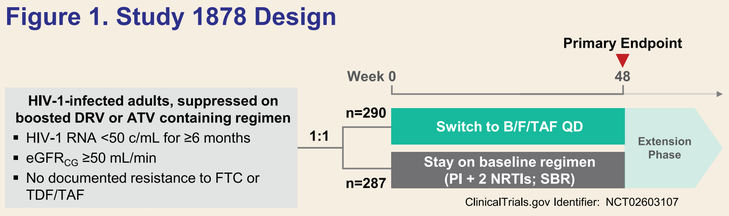
Background

- Bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF) is approved by the US FDA and EMA for treatment of HIV-1 infection (treatment-naïve and virologically suppressed without resistance)[1,2]
  - Five Phase 3 studies of 1440 participants demonstrated safety and efficacy without development of resistance to B/F/TAF through 48 weeks[3-7]
- M184V/I is the most common NRTI substitution in patients with virologic failure to 3TC or FTC
  - Occurs in up to 64% of patients after failure[8-9]
  - Confers resistance to 3TC and FTC and decreases susceptibility to ABC, but increases susceptibility to TFV[10]
  - May not preclude response to triple therapy regimens containing FTC and tenofovir (TFV) in either prodrug form (TDF or TAF)[10-11]
  - May be under-reported by the GenoSure Archive assay[11]
- Viral blips (transient viral load values above the assay limit) can occur in successfully treated patients[12]
  - May reflect residual viral replication, random biological fluctuation, or assay variation[13]
  - May be a marker for future virologic failure, but impacts on clinical outcomes are conflicting[13-15]

Methods

Figure 1. Study 1878 Design



3TC = lamivudine; ABC = abacavir; ATV = atazanavir; c/mL = copies per milliliter; COBI = cobicistat; DRV = darunavir; eGFR = estimated glomerular filtration rate; FTC = emtricitabine; NRTI = nucleos(t)ide reverse transcriptase inhibitor; RTV = ritonavir; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate

Resistance Assessments at Enrollment

- Historical plasma RNA genotypes
  - Collected if available
  - Not required for study entry
  - Documented preexisting M184V/I was excluded if identified prior to randomization
- Whole blood was collected at baseline for potential proviral DNA archive genotyping

Baseline Genotypic Analyses

- Proviral DNA genotype (GenoSure Archive, Monogram Biosciences)
  - Stored baseline samples retrospectively tested
  - All participants in the B/F/TAF treatment group
  - Participants with M184V/I detected post-randomization continued in study and included in all efficacy analyses
- Baseline genotypes
  - Cumulative data from all historical + proviral genotypes
  - Analyzed for preexisting M184V/I and other RT resistance substitutions

Table 1. HIV-1 Drug Resistance Substitutions in Reverse Transcriptase

Resistance Category	Primary RT Amino Acid Substitutions (based on IAS-USA[16])
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

NRTI-R = nucleos(t)ide RT inhibitor resistance; NNRTI-R = nonnucleoside RT inhibitor resistance; RT = reverse transcriptase; TAMs = thymidine analog-associated mutations

Blip Analyses

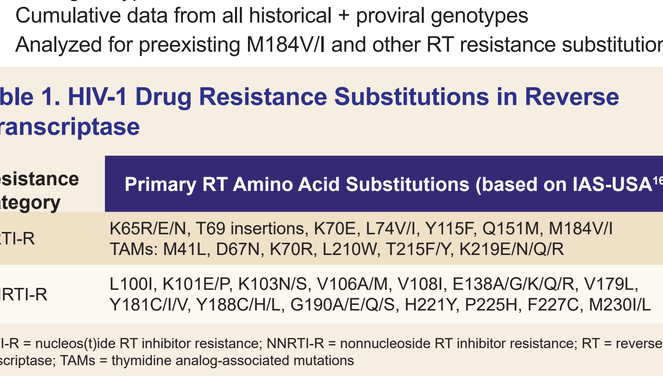
- Plasma HIV-1 RNA (Roche TaqMan 2.0 test, Roche Diagnostics)
- All on-treatment HIV-1 RNA and outcome data through Week 48 were included
- Viral blip: after the baseline visit, a single HIV-1 RNA value ≥50 c/mL, preceded and followed by HIV-1 RNA <50 c/mL

Statistical Analyses

- Efficacy outcome: proportion of participants with virologic suppression (HIV-1 RNA <50 c/mL) at last on-treatment visit through Week 48
  - Missing HIV-1 RNA values at Week 48 were imputed using the last observation carried forward (LOCF) method
  - Distinct from Week 48 snapshot analysis
- Statistical comparisons were performed using Student's t-test, Fisher's exact test, or Cochran-Mantel-Haenszel test as appropriate

Results

Figure 2. Baseline Genotypic Data Sources and M184V/I Detection in the B/F/TAF Group



a. Insufficient sample available for testing (n=9) or proviral genotyping assay failure (n=9).
b. Insufficient sample available for testing (n=6) or proviral genotyping assay failure (n=7) and no historical genotype available

- In the B/F/TAF group, pre-switch (baseline) genotypic data were obtained for 277 of 290 (96%) participants
  - No M184V/I by historical genotype as this was exclusionary
  - All 42 cases of M184V/I were detected by proviral genotyping and previously undocumented

Results (cont'd)

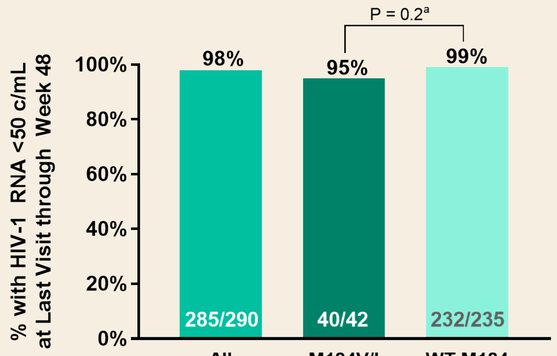
Table 2. Baseline Characteristics Stratified by M184V/I Detection

		B/F/TAF Any Baseline Data[a] (n=277)		
		M184V/I (n=42)	Wild-type M184 (n=235)	P value[b]
Mean age, years (range)		**51 (29–65)**	**46 (20–74)**	**0.003**
Male, % (n)		81% (34)	85% (200)	0.5
Mean CD4 count, cells/μL (range)		648 (217–1415)	673 (147–2582)	0.6
HIV-1 subtype B, % (n)		98% (41)	90% (211)	0.1
Mean time since ARV initiation, years (range)		**15 (3–29)**	**9 (1–29)**	**<0.001**
Mean time on boosted PI regimen, years (range)		7 (0.9–20)	6 (0.6–20)	0.08
Baseline ARV regimen, % (n)				
NRTI	FTC/TDF	76% (32)	86% (201)	0.2
	ABC/3TC	24% (10)	14% (34)	
Boosted PI	DRV	45% (19)	60% (141)	0.1
	ATV	52% (23)	40% (94)	

a. Participants with historical genotypic data only were assumed to have wild-type M184
b. P values for mean data calculated by Student's t-test (2-tailed). P values for percentage data calculated by Fisher's Exact test.

- Presence of proviral M184V/I was associated with longer time since ARV initiation compared to wild-type M184
  - But some participants with M184V/I initiated ARV as few as 3 years ago

Figure 3. Virologic Suppression at Last On-treatment Visit through Week 48 Stratified by M184V/I Detection



a. P value calculated by Fisher's exact test
WT = wild-type

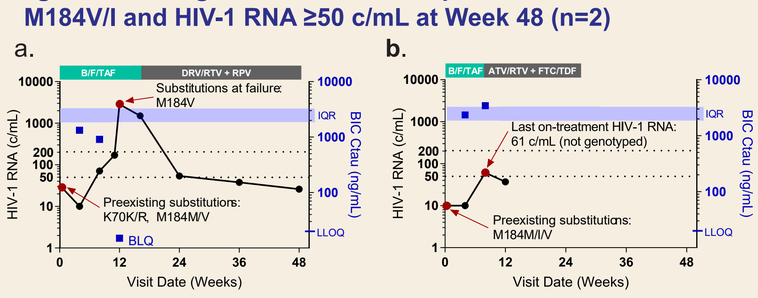
Table 3. Baseline Resistance Frequencies and Virologic Suppression at Last On-treatment Visit through Week 48

	Percent of Participants (n/N)	
Baseline Resistance Category	B/F/TAF Any Baseline Data (n=277)	HIV-1 RNA <50 c/mL at Last Visit through Week 48
M184 substitutions	**15% (42/277)**	**95% (40/42)[a]**
V only	88% (37/42)	97% (36/37)
I only	7% (3/42)	100% (3/3)
V/I mixture	5% (2/42)	50% (1/2)
Any NRTI-R	**22% (61/277)**	**95% (58/61)**
M184V/I only	43% (26/61)	96% (25/26)
M184V/I + other NRTI-R	26% (16/61)	94% (15/16)
M184V/I + TAMs	21% (13/61)	92% (12/13)
Other NRTI-R only	31% (19/61)	95% (18/19)
Any NNRTI-R	**29% (79/277)**	**100% (79/79)**
M184V/I + NNRTI-R	28% (22/79)	100% (22/22)
Wild-type M184 + NNRTI-R	72% (57/79)	100% (57/57)

a. 2 participants with preexisting M184V/I had HIV-1 RNA ≥50 c/mL at their last visit through Week 48 and are described in further detail in Figure 4

- High rates (95% -100%) of virologic suppression on B/F/TAF were observed among participants with preexisting M184V/I and other RT resistance substitutions
  - Similar to the rate of virologic suppression in the overall B/F/TAF-treated population (98%)

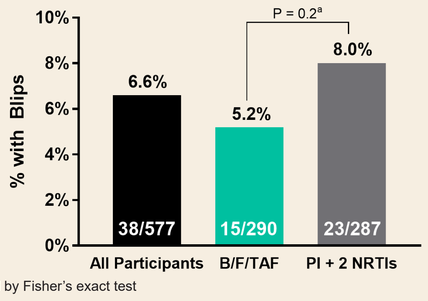
Figure 4. Virologic Profiles of Participants with Proviral M184V/I and HIV-1 RNA ≥50 c/mL at Week 48 (n=2)



- Confirmed virologic failure at Week 12 with HIV-1 RNA 2860 c/mL, BIC concentration BLQ, and no de novo resistance development
- Discontinued B/F/TAF at Week 16 with HIV-1 RNA 1510 c/mL (participant's decision)
- Adherence through discontinuation: 76% by pill count
- Discontinued B/F/TAF at Week 8 with HIV-1 RNA 61 c/mL (participant's decision), too low for resistance testing
- Withdrew study consent at Week 12
- Adherence through discontinuation: 71% by pill count

BIC = bictegravir; BLQ = below limit of quantification; Ctau = concentration at end of dosing interval; IQR = interquartile range (1951 – 3088 ng/mL for BIC Ctau; N = 1193 HIV-1-infected B/F/TAF-treated participants from 4 Phase 3 studies[1,17]); LLOQ = lower limit of quantification (20 c/mL for HIV-1 RNA and 20 ng/mL for BIC Ctau)

Figure 5. Proportion of Participants with Blips



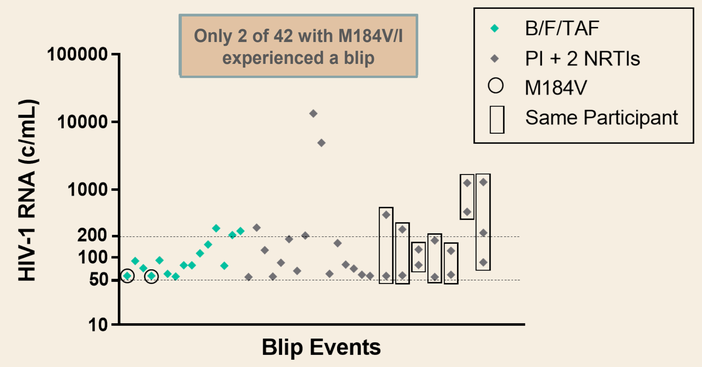
a. P value calculated by Fisher's exact test

- Blips occurred in a similar proportion of participants in both treatment groups
- All participants with blips had virologic suppression at last on-treatment visit through Week 48

Table 4. Proportion of Participants with Blips and Virologic Suppression at Last On-treatment Visit through Week 48

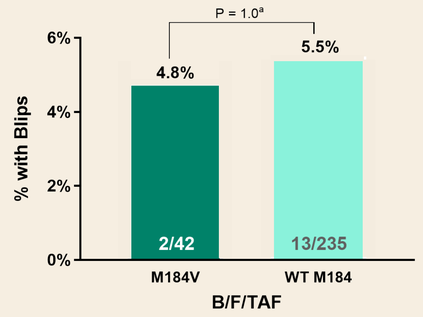
	Percent of Participants (n/N)	
Baseline Resistance Category	B/F/TAF All Participants (n=290)	PI + 2 NRTIs All Participants (n=287)
Experienced Blips	**5.2% (15)**	**8.0% (23)**
1 Blip Event	100% (15/15)	70% (16/23)
2 Blip Events	0	26% (6/23)
3 Blip Events	0	4% (1/23)
HIV-1 RNA <50 c/mL at Last Visit through Week 48	100% (15/15)	100% (23/23)

Figure 6. Viral Load at Blip (46 Blips in 38 Participants)



- The boosted PI group had more blips per participant than the B/F/TAF group (P=0.03 by Cochran-Mantel-Haenszel test)
  - All 15 B/F/TAF-treated participants had 1 blip
  - Participants on boosted PIs had a mean of 1.3 blips

Figure 7. Proportion of B/F/TAF-treated Participants with Blips by Baseline M184V/I



a. P value calculated by Fisher's exact test

- In the B/F/TAF group, blips occurred in a similar proportion of participants with M184V/I or wild-type M184

Conclusions

- Unexpectedly high levels of preexisting M184V/I not detected at screening
  - 15% of participants with any baseline genotypic data had archived M184V/I by retrospective proviral DNA genotype
    - 6% of participants with wild-type M184 by historical genotype had archived M184V/I
    - 26% of participants without historical genotypes had archived M184V/I
  - Both historical and proviral genotypes may help detect M184V/I but sensitivity is limited
- Characteristics associated with archived M184V/I:
  - Participants with M184V/I were older and had longer ARV durations
    - Mean ARV duration was 15 years, but some participants with M184V/I initiated ARV as few as 3 years ago
  - M184V/I often detected with other resistance mutations (38% with other NRTI-R [16/42] and 52% with NNRTI-R [22/42])
- B/F/TAF maintained high levels of HIV-1 RNA suppression, regardless of M184V/I
  - 98% of all participants overall
  - 95% of participants with preexisting M184V/I
  - No treatment-emergent resistance in the B/F/TAF group
- Viral blips were infrequent with B/F/TAF group (5.2%)
  - Similar with or without M184V/I
  - Participants on boosted PIs had more blips than with B/F/TAF group
  - Presence of blips did not alter suppression at Week 48
- A triple therapy regimen of B/F/TAF may be an effective treatment option for suppressed patients with or without evidence of preexisting M184V/I

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Acknowledgments

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